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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

RALICA ZAMFIROVA, RACHAEL MAHER, JASMIN AMARO, MARINA GOMEZ, ANGELE NELSON, REBECCA TORRES, CAROLYN GILL, MARY JO BARNES, TERESA FAUGHNAN, JENNIFER MALTESE, LISA BRADY and KIMBERLY MEFFERT, individually and on behalf of others similarly situated, Plaintiffs, v. AMAG PHARMACEUTICALS, INC., Defendant.	Civil Action No. 2:20-cv-00152-JMV-SCM Honorable John Michael Vazquez Honorable Steven C. Mannion **DECLARATION OF MARC A. MARINACCIO IN SUPPORT OF DEFENDANT AMAG PHARMACEUTICALS, INC.'S MOTION TO DISMISS THE CONSOLIDATED AMENDED COMPLAINT**

I, Marc A. Marinaccio, make this Declaration pursuant to 28 U.S.C. §1746:

1. I am an attorney with Hogan Lovells US LLP, counsel for defendant AMAG Pharmaceuticals, Inc. ("AMAG") in the above-captioned action.

2. The document attached as Exhibit A to AMAG's Motion to Dismiss the Consolidated Amended Complaint is a true and correct copy of the FDA-approved label for Makena, dated February 2018, with pagination added by counsel for the Court's convenience, downloaded on June 5, 2020 from the FDA's website, at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021945s012lbl.pdf.

3. The document attached as Exhibit B to AMAG's Motion to Dismiss the Consolidated Amended Complaint is a true and correct copy of the FDA Briefing Document, NDA 021945, from the Bone, Reproductive, and Urologic Drugs Advisory Committee Meeting, dated October 29, 2019 and downloaded on June 5, 2020 from the FDA website, at: https://www.fda.gov/media/132003/download.

4. The document attached as Exhibit C to AMAG's Motion to Dismiss the Consolidated Amended Complaint is a true and correct copy of AMAG's Press Release, *AMAG Files Response to Citizen Petition*, dated January 21, 2020, with pagination added by counsel for the Court's convenience, downloaded on June 7, 2020 from AMAG's website, at: https://www.amagpharma.com/news/amag-files-response-to-citizen-petition/.

5. The document attached as Exhibit D to AMAG's Motion to Dismiss the Consolidated Amended Complaint is a true and correct copy of screenshots taken on June 7, 2020 from a testimonial video entitled "Watch Kate's story (8:10)" on AMAG's website, at: https://makena.com/reducing-preterm-birth-risk-with-makena/#true-3.

6. The document attached as Exhibit E to AMAG's Motion to Dismiss the Consolidated Amended Complaint is a true and correct copy of the Makena Patient Education Brochure, downloaded on June 5, 2020 from AMAG's website, at: https://makena.com/wp-

content/uploads/2018/11/PP-MKN-US-00363-makena-auto-injector-patient-education-brochure.pdf.

7. The document attached as Exhibit F to AMAG's Motion to Dismiss the Consolidated Amended Complaint is a true and correct copy of a letter AMAG received from Plaintiffs' counsel in this action, dated January 3, 2020.

Pursuant to 28 U.S.C. §1746, I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Date: June 8, 2020

By: /s/ Marc A. Marinaccio

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EXHIBIT A

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use

MAKENA safely and effectively. See full prescribing information for MAKENA.

MAKENA® (hydroxyprogesterone caproate injection) for intramuscular or subcutaneous use

Initial U.S. Approval: 1956

----------RECENT MAJOR CHANGES----------

Dosage and Administration, Dosing (2.1) 02/2018

Dosage and Administration, Preparation & Administration (2.2) 02/2018

----------INDICATIONS AND USAGE----------

Makena is a progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth (1). The effectiveness of Makena is based on improvement in the proportion of women who delivered < 37 weeks of gestation (14). There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity.

Limitation of use: Makena is not intended for use in women with multiple gestations or other risk factors for preterm birth. (1)

----------DOSAGE AND ADMINISTRATION----------

- Makena auto-injector: Administer subcutaneously using Makena auto-injector at a dose of 275 mg (1.1 mL) once weekly, in the back of either upper arm (2.1)
- Makena (single- and multi-dose vials): Administer intramuscularly at a dose of 250 mg (1 mL) once weekly in the upper outer quadrant of the gluteus maximus (2.1)
- Begin treatment between 16 weeks, 0 days and 20 weeks, 6 days of gestation (2.1)
- Continue administration once weekly until week 37 (through 36 weeks, 6 days) of gestation or delivery, whichever occurs first (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

1.1 mL single-use auto-injector for subcutaneous use contains 275 mg of hydroxyprogesterone caproate (250 mg/mL) (3)

1 mL single-dose vial for intramuscular use contains 250 mg of hydroxyprogesterone caproate. (3)

5 mL multi-dose vial for intramuscular use contains 1250 mg of hydroxyprogesterone caproate (250 mg/mL). (3)

----------CONTRAINDICATIONS----------

- Current or history of thrombosis or thromboembolic disorders (4)
- Known or suspected breast cancer, other hormone-sensitive cancer, or history of these conditions (4)
- Undiagnosed abnormal vaginal bleeding unrelated to pregnancy (4)
- Cholestatic jaundice of pregnancy (4)
- Liver tumors, benign or malignant, or active liver disease (4)
- Uncontrolled hypertension (4)

----------WARNINGS AND PRECAUTIONS----------

- Thromboembolic disorders: Discontinue if thrombosis or thromboembolism occurs (5.1)
- Allergic reactions: Consider discontinuing if allergic reactions occur (5.2)
- Decreased glucose tolerance: Monitor prediabetic and diabetic women receiving Makena (5.3)
- Fluid retention: Monitor women with conditions that may be affected by fluid retention, such as preeclampsia, epilepsy, cardiac or renal dysfunction (5.4)
- Depression: Monitor women with a history of clinical depression; discontinue Makena if depression recurs (5.5)

----------ADVERSE REACTIONS----------

- In a study where the Makena instramuscular injection was compared with placebo, the most common adverse reactions reported with Makena intramuscular injection (reported incidence in ≥ 2% of subjects and higher than in the control group) were: injection site reactions (pain [35%], swelling [17%], pruritus [6%], nodule [5%]), urticaria (12%), pruritus (8%), nausea (6%), and diarrhea (2%). (6.1)
- In studies where the Makena subcutaneous injection using auto-injector was compared with Makena intramuscular injection, the most common adverse reaction reported with Makena auto-injector use (and higher than with Makena intramuscular injection)-was injection site pain (10% in one study and 34% in another). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AMAG Pharmaceuticals at 1-877-411-2510 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised 02/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Makena is a progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. The effectiveness of Makena is based on improvement in the proportion of women who delivered < 37 weeks of gestation. There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity.

Limitation of use: While there are many risk factors for preterm birth, safety and efficacy of Makena has been demonstrated only in women with a prior spontaneous singleton preterm birth. **It is not intended for use in women with multiple gestations or other risk factors for preterm birth.**

2 DOSAGE AND ADMINISTRATION

2.1 Dosing

- Makena auto-injector: Administer **subcutaneously** using auto-injector at a dose of 275 mg (1.1 mL) once weekly (every 7 days) in the back of either upper arm by a healthcare provider
- Makena (single- and multi-dose vials): Administer **intramuscularly** at a dose of 250 mg (1 mL) once weekly (every 7 days) in the upper outer quadrant of the gluteus maximus by a healthcare provider
- Begin treatment between 16 weeks, 0 days and 20 weeks, 6 days of gestation
- Continue administration once weekly until week 37 (through 36 weeks, 6 days) of gestation or delivery, whichever occurs first

2.2 Preparation and Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Makena is a clear, yellow solution. The solution must be clear at the time of use; replace vial if visible particles or crystals are present.

Specific instructions for administration by dosage form:

Makena single-dose or multi-dose vials (intramuscular use only)

Makena single-dose or multi-dose vials are only for intramuscular injection with a syringe into the upper outer quadrant of the gluteus maximus, rotating the injection site to the alternate side from the previous week, using the following preparation and administration procedure:

1. Clean the vial top with an alcohol swab before use.

2. Draw up 1 mL of drug into a 3 mL syringe with an 18 gauge needle.
3. Change the needle to a 21 gauge 1½ inch needle.
4. After preparing the skin, inject in the upper outer quadrant of the gluteus maximus. The solution is viscous and oily. Slow injection (over one minute or longer) is recommended.
5. Applying pressure to the injection site may minimize bruising and swelling.

If the 5 mL multi-dose vial is used, discard any unused product 5 weeks after first use.

Makena auto-injector (subcutaneous use only)

Makena auto-injector is a single-use, pre-filled, disposable device containing a 27 gauge, 0.5 inch needle that delivers one dose subcutaneously in the back of the upper arm.

Because Makena auto-injector is preservative-free, once the cap is removed the device should be used immediately or discarded.

Rotate the injection site to the alternate arm from the previous week. Do not use in areas where the skin is tender, bruised, red, scaly, raised, thick, or hard. Avoid areas with scars, tattoos, or stretch marks.

The solution is viscous and oily. The auto-injector takes approximately 15 seconds to deliver the dose; when the viewing window is fully blocked (completely orange), the full dose has been administered.

The "Instructions for Use" contains detailed steps for administering the subcutaneous injection using the auto-injector [*see Dosage and Administration (2.3)*]. Read the "Instructions for Use" carefully before administering Makena auto-injector.

2.3 Instructions for Use (Makena Auto-injector)

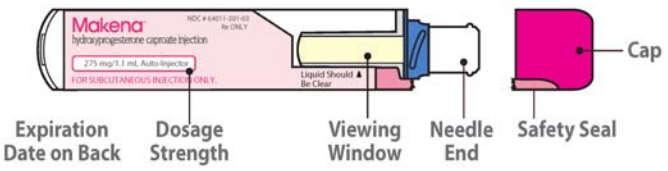
Instructions for Use: Read this carefully before each use.

FOR SUBCUTANEOUS USE ONLY

Makena®
hydroxyprogesterone caproate injection
275 mg/1.1 mL (250 mg/mL) Auto-Injector

For subcutaneous injection.
Single Use.
Administer one injection weekly.
Administration by Healthcare Professionals only.

Description of Parts



Preparation

If you need help or instructions, call:
1-800-411-2510

- Carefully read all steps before beginning injection.
- Injection process must be completed without interruption.

Supplies You Will Need

- 1 Makena Auto-Injector
- 1 alcohol swab
- 1 cotton ball or gauze

Storage Conditions

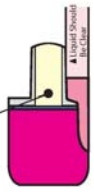
- DO NOT refrigerate or freeze.
- Protect from light.
- Store at 20° - 25°C (68° - 77° F).
- Keep away from children.

1 Inspect Makena Auto-Injector

- Inspect the Makena Auto-Injector for any visible damage. **DO NOT** use if it appears damaged or broken, or if cap is missing or not secure.
- Check the expiration date. **DO NOT** use if expired.
- Inspect the medication liquid through the Viewing Window; it should be clear to light yellow and free of particles. **(See Figure 1).**

DO NOT use if the liquid is cloudy or if particles are present. You may notice an air bubble, this is normal.

Figure 1:



2 Select & Prepare Subcutaneous Injection Site

Only use the back of either upper arm for injection site.

- Rotate the injection site to the alternate arm from the previous week. **(See Figure 2).**
- Wash your hands with soap and water. ▶ Wipe the injection site with an alcohol swab.
- Allow the site to dry on its own. **DO NOT** fan or blow on the injection site. **DO NOT** touch the site again before injecting.

DO NOT use in areas where the skin is tender, bruised, red, scaly, raised, thick, or hard.
Avoid areas with scars, tattoos, or stretch marks.

Figure 2:

INJECT SUBCUTANEOUSLY IN THE BACK OF EITHER UPPER ARM

Administering Subcutaneous Injection

3 Remove Cap

- Twist the cap counter clockwise (this will break the red safety seal), and pull cap straight off. **(See Figure 3).**

After the cap is removed, a few drops of liquid may appear - this is normal.
Auto-Injector should be used or discarded once cap is removed.
DO NOT recap for later use. **DO NOT** use if device is dropped.

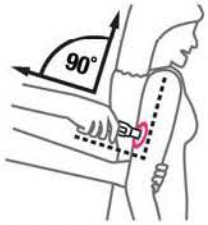
Figure 3: TWIST THEN PULL

DO NOT touch or try to remove Needle End of Auto-Injector after cap is removed, doing so can cause injury.

4 Position Makena Auto-Injector

- Support the upper arm with the opposite hand. **(See Figure 4).**
- On the relaxed outstretched arm to be injected, gently place the Makena Auto-Injector at a 90˚ angle to the injection site (back of upper arm, **See Figure 4**).
- Check that you can see the viewing window clearly.

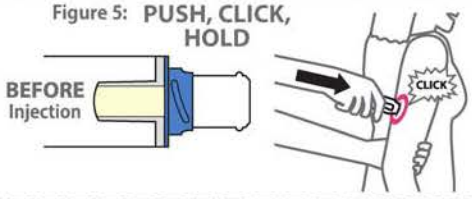
Figure 4:



5 Begin Injection

- It will take approximately 15 seconds for the full dose to be delivered.
  - Push down while supporting the upper arm with the opposite hand. A click will occur when the injection begins. **(See figure 5).**
  - Hold the Auto-Injector against the arm.

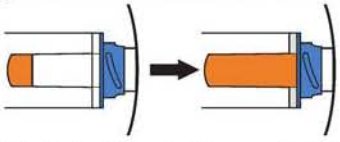
Figure 5: PUSH, CLICK, HOLD



6 Complete Injection

- While holding against the arm, watch the viewing window until it turns orange Verify viewing window has turned completely orange before removing from injection site.
- It is normal if there is slight bleeding after injection. If this occurs, hold a cotton ball or gauze on the area with light pressure for a few seconds. **DO NOT** rub the area.

Figure 6: WATCH VIEWING WINDOW



- **A fully blocked (completely orange) window confirms the dose was administered.**

If the Viewing Window is not blocked:
- **DO NOT** use another Makena Auto-Injector or attempt another injection.
- **Call 1-877-411-2510** for assistance.

Record the location of the injection site in the patient's record to ensure rotation of the injection site each week.

7 Disposal After Injection

- After completing injection, dispose of Makena Auto-Injector and cap in a sharps disposal container immediately after use.

FOR POSITION ONLY
128 Barcode

Distributed by: AMAG Pharmaceuticals, Inc.
Waltham, MA 02451

900232-001 rev04

3 DOSAGE FORMS AND STRENGTHS

Subcutaneous injection: 275 mg/1.1 mL clear yellow solution in single-use auto-injector.

Intramuscular injection: 250 mg/mL clear yellow solution in single-dose vials.

Intramuscular injection: 1250 mg/5 mL (250 mg/mL) clear yellow solution in multiple-dose vials.

4 CONTRAINDICATIONS

Do not use Makena in women with any of the following conditions:

- Current or history of thrombosis or thromboembolic disorders
- Known or suspected breast cancer, other hormone-sensitive cancer, or history of these conditions
- Undiagnosed abnormal vaginal bleeding unrelated to pregnancy
- Cholestatic jaundice of pregnancy
- Liver tumors, benign or malignant, or active liver disease
- Uncontrolled hypertension

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders

Discontinue Makena if an arterial or deep venous thrombotic or thromboembolic event occurs.

5.2 Allergic Reactions

Allergic reactions, including urticaria, pruritus and angioedema, have been reported with use of Makena or with other products containing castor oil. Consider discontinuing the drug if such reactions occur.

5.3 Decrease in Glucose Tolerance

A decrease in glucose tolerance has been observed in some patients on progestin treatment. The mechanism of this decrease is not known. Carefully monitor prediabetic and diabetic women while they are receiving Makena.

5.4 Fluid Retention

Because progestational drugs may cause some degree of fluid retention, carefully monitor women with conditions that might be influenced by this effect (e.g., preeclampsia, epilepsy, migraine, asthma, cardiac or renal dysfunction).

5.5 Depression

Monitor women who have a history of clinical depression and discontinue Makena if clinical depression recurs.

5.6 Jaundice

Carefully monitor women who develop jaundice while receiving Makena and consider whether the benefit of use warrants continuation.

5.7 Hypertension

Carefully monitor women who develop hypertension while receiving Makena and consider whether the benefit of use warrants continuation.

6 ADVERSE REACTIONS

For the most serious adverse reactions to the use of progestins, see *Warnings and Precautions (5)*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In a vehicle (placebo)-controlled clinical trial of 463 pregnant women at risk for spontaneous preterm delivery based on obstetrical history, 310 received 250 mg of Makena and 153 received a vehicle formulation containing no drug by a weekly intramuscular injection beginning at 16 to 20 weeks of gestation and continuing until 37 weeks of gestation or delivery, whichever occurred first. [*See Clinical Studies (14.1)*.]

Certain pregnancy-related fetal and maternal complications or events were numerically increased in the Makena-treated subjects as compared to control subjects, including miscarriage and stillbirth, admission for preterm labor, preeclampsia or gestational hypertension, gestational diabetes, and oligohydramnios (Tables 1 and 2).

Table 1 Selected Fetal Complications

Pregnancy Complication	**Makena n/N**	**Control n/N**
Miscarriage (< 20 weeks)[1]	5/209	0/107
Stillbirth (≥ 20 weeks)[2]	6/305	2/153

[1] N = Total number of subjects enrolled prior to 20 weeks 0 days
[2] N = Total number of subjects at risk ≥ 20 weeks

Table 2 Selected Maternal Complications

Pregnancy Complication	Makena N=310 %	Control N=153 %
Admission for preterm labor[1]	16.0	13.8
Preeclampsia or gestational hypertension	8.8	4.6
Gestational diabetes	5.6	4.6
Oligohydramnios	3.6	1.3

[1] Other than delivery admission.

Common Adverse Reactions:

The most common adverse reaction with intramuscular injection was injection site pain, which was reported after at least one injection by 34.8% of the Makena group and 32.7% of the control group. Table 3 lists adverse reactions that occurred in ≥ 2% of subjects and at a higher rate in the Makena group than in the control group.

Table 3 Adverse Reactions Occurring in ≥ 2% of Makena-Treated Subjects and at a Higher Rate than Control Subjects

Preferred Term	Makena N=310 %	Control N=153 %
Injection site pain	34.8	32.7
Injection site swelling	17.1	7.8
Urticaria	12.3	11.1
Pruritus	7.7	5.9
Injection site pruritus	5.8	3.3
Nausea	5.8	4.6
Injection site nodule	4.5	2.0
Diarrhea	2.3	0.7

In the clinical trial using intramuscular injection, 2.2% of subjects receiving Makena were reported as discontinuing therapy due to adverse reactions compared to 2.6% of control subjects. The most common adverse reactions that led to discontinuation in both groups were urticaria and injection site pain/swelling (1% each).

Pulmonary embolus in one subject and injection site cellulitis in another subject were reported as serious adverse reactions in Makena-treated subjects.

Two clinical studies were conducted in healthy post-menopausal women, comparing Makena administered via subcutaneous auto-injector to Makena administered as an intramuscular injection. In the first study, injection site pain occurred in 3/30 (10%) of subjects who used the subcutaneous auto-injector vs. 2/30 (7%) of subjects receiving intramuscular injection. In the

second study, injection site pain occurred in 20/59 (34%) of subjects who used the subcutaneous auto-injector vs. 5/61 (8%) of subjects receiving intramuscular injection.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Makena. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Body as a whole*: Local injection site reactions (including erythema, urticaria, rash, irritation, hypersensitivity, warmth); fatigue; fever; hot flashes/flushes
- *Digestive disorders*: Vomiting
- *Infections*: Urinary tract infection
- *Nervous system disorders*: Headache, dizziness
- *Pregnancy, puerperium and perinatal conditions:* Cervical incompetence, premature rupture of membranes
- *Reproductive system and breast disorders:* Cervical dilation, shortened cervix
- *Respiratory disorders*: Dyspnea, chest discomfort
- *Skin*: Rash

7 DRUG INTERACTIONS

In vitro drug-drug interaction studies were conducted with Makena. Hydroxyprogesterone caproate has minimal potential for CYP1A2, CYP2A6, and CYP2B6 related drug-drug interactions at the clinically relevant concentrations. *In vitro* data indicated that therapeutic concentration of hydroxyprogesterone caproate is not likely to inhibit the activity of CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 [*See Clinical Pharmacology (12.3).*] No *in vivo* drug-drug interaction studies were conducted with Makena.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Makena is indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. Fetal, neonatal, and maternal risks are discussed throughout labeling. Data from the placebo-controlled clinical trial and the infant follow-up safety study [*see Clinical Studies (14.1, 14.2)*] did not show a difference in adverse developmental outcomes between children of Makena-treated women and children of control subjects. However, these data are insufficient to determine a drug-associated risk of adverse developmental outcomes as none of the Makena-treated women received the drug during the first trimester of pregnancy. In animal reproduction studies, intramuscular administration of hydroxyprogesterone caproate to pregnant rats during gestation at doses 5 times the human dose equivalent based on a 60-kg human was not associated with adverse developmental outcomes.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Reproduction studies of hydroxyprogesterone caproate administered to various animal species have been reported in the literature. In nonhuman primates, embryolethality was reported in rhesus monkeys administered hydroxyprogesterone caproate up to 2.4 and 24 times the human dose equivalent, but not in cynomolgus monkeys administered hydroxyprogesterone caproate at doses up to 2.4 times the human dose equivalent, every 7 days between days 20 and 146 of gestation. There were no teratogenic effects in either strain of monkey.

Reproduction studies have been performed in mice and rats at doses up to 95 and 5, respectively, times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to hydroxyprogesterone caproate.

8.2 Lactation

Risk Summary

Low levels of progestins are present in human milk with the use of progestin-containing products, including hydroxyprogesterone caproate. Published studies have reported no adverse effects of progestins on the breastfed child or on milk production.

8.4 Pediatric Use

Makena is not indicated for use in women under 16 years of age. Safety and effectiveness in patients less than 16 years of age have not been established. A small number of women under age 18 years were studied; safety and efficacy are expected to be the same in women aged 16 years and above as for users 18 years and older [*see Clinical Studies (14)*].

8.6 Hepatic Impairment

No studies have been conducted to examine the pharmacokinetics of Makena in patients with hepatic impairment. Makena is extensively metabolized and hepatic impairment may reduce the elimination of Makena.

10 OVERDOSAGE

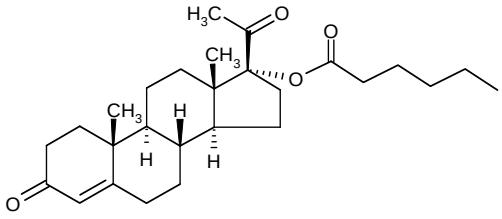
There have been no reports of adverse events associated with overdosage of Makena in clinical trials. In the case of overdosage, the patient should be treated symptomatically.

11 DESCRIPTION

The active pharmaceutical ingredient in Makena is hydroxyprogesterone caproate, a progestin.

The chemical name for hydroxyprogesterone caproate is pregn-4-ene-3,20-dione, 17[(1-oxohexyl)oxy]. It has an empirical formula of $C_{27}H_{40}O_4$ and a molecular weight of 428.60. Hydroxyprogesterone caproate exists as white to practically white crystals or powder with a melting point of 120°-124°C.

The structural formula is:



Makena is a clear, yellow, sterile, non-pyrogenic solution for intramuscular (vials) or subcutaneous (auto-injector) injection. Each 1.1 mL Makena auto-injector for subcutaneous use and each 1 mL single-dose vial for intramuscular use contains hydroxyprogesterone caproate USP, 250 mg/mL (25% w/v), in a preservative-free solution containing castor oil USP (30.6% v/v) and benzyl benzoate USP (46% v/v). Each 5 mL multi-dose vial contains hydroxyprogesterone caproate USP, 250 mg/mL (25% w/v), in castor oil USP (28.6%) and benzyl benzoate USP (46% v/v) with the preservative benzyl alcohol NF (2% v/v).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Hydroxyprogesterone caproate is a synthetic progestin. The mechanism by which hydroxyprogesterone caproate reduces the risk of recurrent preterm birth is not known.

12.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted with Makena.

12.3 Pharmacokinetics

Absorption: Female patients with a singleton pregnancy received intramuscular doses of 250 mg hydroxyprogesterone caproate for the reduction of preterm birth starting between 16 weeks 0 days and 20 weeks 6 days. All patients had blood drawn daily for 7 days to evaluate pharmacokinetics.

Table 4 Summary of Mean (Standard Deviation) Pharmacokinetic Parameters for Hydroxyprogesterone Caproate

Group (N)	C_{max} (ng/mL)	T_{max} (days)[a]	$AUC_{(0-t)}$[b] (ng·hr/mL)
Group 1 (N=6)	5.0 (1.5)	5.5 (2.0-7.0)	571.4 (195.2)
Group 2 (N=8)	12.5 (3.9)	1.0 (0.9-1.9)	1269.6 (285.0)
Group 3 (N=11)	12.3 (4.9)	2.0 (1.0-3.0)	1268.0 (511.6)

Blood was drawn daily for 7 days (1) starting 24 hours after the first dose between Weeks 16-20 (Group 1), (2) after a dose between Weeks 24-28 (Group 2), or (3) after a dose between Weeks 32-36 (Group 3)

[a] Reported as median (range)

[b] t = 7 days

For all three groups, peak concentration (C_{max}) and area under the curve ($AUC_{(1\text{-}7\ days)}$) of the mono-hydroxylated metabolites were approximately 3-8-fold lower than the respective

parameters for the parent drug, hydroxyprogesterone caproate. While di-hydroxylated and tri-hydroxylated metabolites were also detected in human plasma to a lesser extent, no meaningful quantitative results could be derived due to the absence of reference standards for these multiple hydroxylated metabolites. The relative activity and significance of these metabolites are not known.

The elimination half-life of hydroxyprogesterone caproate, as evaluated from 4 patients in the study who reached full-term in their pregnancies, was 16.4 (±3.6) days. The elimination half-life of the mono-hydroxylated metabolites was 19.7 (±6.2) days.

In a single-dose, open-label, randomized, parallel design bioavailability study in 120 healthy post-menopausal women, comparable systemic exposure of hydroxyprogesterone caproate was seen when Makena was administered subcutaneously with the auto-injector (1.1 mL) in the back of the upper arm and when Makena was dosed intramuscularly (1 mL) in the upper outer quadrant of the gluteus maximus.

Distribution: Hydroxyprogesterone caproate binds extensively to plasma proteins including albumin and corticosteroid binding globulins.

Metabolism: In vitro studies have shown that hydroxyprogesterone caproate can be metabolized by human hepatocytes, both by phase I and phase II reactions. Hydroxyprogesterone caproate undergoes extensive reduction, hydroxylation and conjugation. The conjugated metabolites include sulfated, glucuronidated and acetylated products. In vitro data indicate that the metabolism of hydroxyprogesterone caproate is predominantly mediated by CYP3A4 and CYP3A5. The in vitro data indicate that the caproate group is retained during metabolism of hydroxyprogesterone caproate.

Excretion: Both conjugated metabolites and free steroids are excreted in the urine and feces, with the conjugated metabolites being prominent. Following intramuscular administration to pregnant women at 10-12 weeks gestation, approximately 50% of a dose was recovered in the feces and approximately 30% recovered in the urine.

Drug Interactions

Cytochrome P450 (CYP) enzymes: An *in vitro* inhibition study using human liver microsomes and CYP isoform-selective substrates indicated that hydroxyprogesterone caproate increased the metabolic rate of CYP1A2, CYP2A6, and CYP2B6 by approximately 80%, 150%, and 80%, respectively. However, in another *in vitro* study using human hepatocytes under conditions where the prototypical inducers or inhibitors caused the anticipated increases or decreases in CYP enzyme activities, hydroxyprogesterone caproate did not induce or inhibit CYP1A2, CYP2A6, or CYP2B6 activity. Overall, the findings indicate that hydroxyprogesterone caproate has minimal potential for CYP1A2, CYP2A6, and CYP2B6 related drug-drug interactions at the clinically relevant concentrations.

In vitro data indicated that therapeutic concentration of hydroxyprogesterone caproate is not likely to inhibit the activity of CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Hydroxyprogesterone caproate has not been adequately evaluated for carcinogenicity.

No reproductive or developmental toxicity or impaired fertility was observed in a multigenerational study in rats. Hydroxyprogesterone caproate administered intramuscularly, at gestational exposures up to 5 times the recommended human dose, had no adverse effects on the parental (F_0) dams, their developing offspring (F_1), or the latter offspring's ability to produce a viable, normal second (F_2) generation.

14 CLINICAL STUDIES

14.1 Clinical Trial to Evaluate Reduction of Risk of Preterm Birth

In a multicenter, randomized, double-blind, vehicle (placebo)-controlled clinical trial, the safety and effectiveness of Makena for the reduction of the risk of spontaneous preterm birth was studied in women with a singleton pregnancy (age 16 to 43 years) who had a documented history of singleton spontaneous preterm birth (defined as delivery at less than 37 weeks of gestation following spontaneous preterm labor or premature rupture of membranes). At the time of randomization (between 16 weeks, 0 days and 20 weeks, 6 days of gestation), an ultrasound examination had confirmed gestational age and no known fetal anomaly. Women were excluded for prior progesterone treatment or heparin therapy during the current pregnancy, a history of thromboembolic disease, or maternal/obstetrical complications (such as current or planned cerclage, hypertension requiring medication, or a seizure disorder).

A total of 463 pregnant women were randomized to receive either Makena (N=310) or vehicle (N=153) at a dose of 250 mg administered weekly by intramuscular injection starting between 16 weeks, 0 days and 20 weeks, 6 days of gestation, and continuing until 37 weeks of gestation or delivery. Demographics of the Makena-treated women were similar to those in the control group, and included: 59.0% Black, 25.5% Caucasian, 13.9% Hispanic and 0.6% Asian. The mean body mass index was 26.9 kg/m^2.

The proportions of women in each treatment arm who delivered at < 37 (the primary study endpoint), < 35, and < 32 weeks of gestation are displayed in Table 5.

Table 5 Proportion of Subjects Delivering at < 37, < 35 and < 32 Weeks Gestational Age (ITT Population)

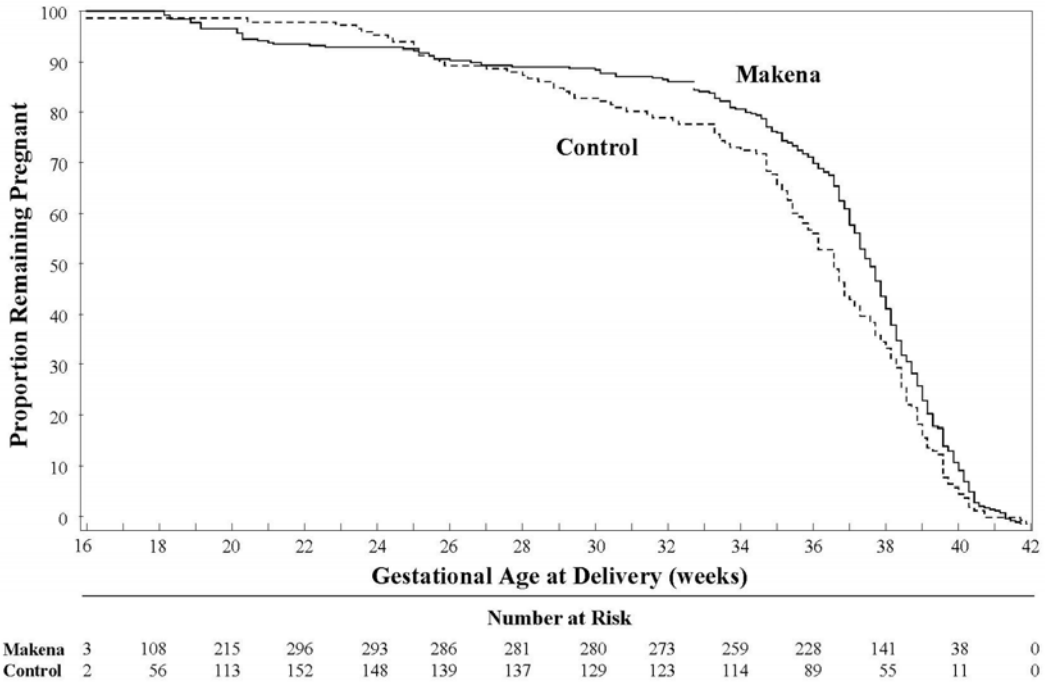
Delivery Outcome	Makena[1] (N=310) %	Control (N=153) %	Treatment difference and 95% Confidence Interval[2]
<37 weeks	37.1	54.9	-17.8% [-28.0%, -7.4%]
<35 weeks	21.3	30.7	-9.4% [-19.0%, -0.4%]
<32 weeks	11.9	19.6	-7.7% [-16.1%, -0.3%]

[1] Four Makena-treated subjects were lost to follow-up. They were counted as deliveries at their gestational ages at time of last contact (18^4, 22^0, 34^3 and 36^4 weeks).
[2] Adjusted for interim analysis.

Compared to controls, treatment with Makena reduced the proportion of women who delivered preterm at < 37 weeks. The proportions of women delivering at < 35 and < 32 weeks also were lower among women treated with Makena. The upper bounds of the confidence intervals for the treatment difference at < 35 and < 32 weeks were close to zero. Inclusion of zero in a confidence interval would indicate the treatment difference is not statistically significant. Compared to the other gestational ages evaluated, the number of preterm births at < 32 weeks was limited.

After adjusting for time in the study, 7.5% of Makena-treated subjects delivered prior to 25 weeks compared to 4.7% of control subjects; see Figure 1.

Figure 1 Proportion of Women Remaining Pregnant as a Function of Gestational Age



The rates of fetal losses and neonatal deaths in each treatment arm are displayed in Table 6. Due to the higher rate of miscarriages and stillbirths in the Makena arm, there was no overall survival difference demonstrated in this clinical trial.

Table 6 Fetal Losses and Neonatal Deaths

Complication	**Makena N=306 [A] n (%) [B]**	**Control N=153 n (%) [B]**
Miscarriages <20 weeks gestation [C]	5 (2.4)	0
Stillbirth	6 (2.0)	2 (1.3)
Antepartum stillbirth	*5 (1.6)*	*1 (0.6)*
Intrapartum stillbirth	*1 (0.3)*	*1 (0.6)*
Neonatal deaths	8 (2.6)	9 (5.9)
Total Deaths	**19 (6.2)**	**11 (7.2)**

[A] Four of the 310 Makena-treated subjects were lost to follow-up and stillbirth or neonatal status could not be determined

[B] Percentages are based on the number of enrolled subjects and not adjusted for time on drug

[C] Percentage adjusted for the number of at risk subjects (n=209 for Makena, n=107 for control) enrolled at <20 weeks gestation.

A composite neonatal morbidity/mortality index evaluated adverse outcomes in live births. It was based on the number of neonates who died or experienced respiratory distress syndrome, bronchopulmonary dysplasia, grade 3 or 4 intraventricular hemorrhage, proven sepsis, or necrotizing enterocolitis. Although the proportion of neonates who experienced 1 or more events was numerically lower in the Makena arm (11.9% vs. 17.2%), the number of adverse outcomes was limited and the difference between arms was not statistically significant.

14.2 Infant Follow-Up Safety Study

Infants born to women enrolled in this study, and who survived to be discharged from the nursery, were eligible for participation in a follow-up safety study. Of 348 eligible offspring, 79.9% enrolled: 194 children of Makena-treated women and 84 children of control subjects. The primary endpoint was the score on the Ages & Stages Questionnaire (ASQ), which evaluates communication, gross motor, fine motor, problem solving, and personal/social parameters. The proportion of children whose scores met the screening threshold for developmental delay in each developmental domain was similar for each treatment group.

16 HOW SUPPLIED/STORAGE AND HANDLING

Makena auto-injector (for subcutaneous injection)

Makena auto-injector (NDC 64011-301-03) is supplied as 1.1 mL of a clear yellow sterile preservative-free solution in an auto-injector containing a pre-filled syringe. Each 1.1 mL auto-injector contains hydroxyprogesterone caproate USP, 250 mg/mL (25% w/v), in castor oil USP (30.6% v/v) and benzyl benzoate USP (46% v/v).

Single unit carton: Contains one 1.1 mL single-patient-use auto-injector of Makena containing 275 mg of hydroxyprogesterone caproate.

Store at 20° to 25°C (68° to 77°F). Do not refrigerate or freeze.

Caution: Protect auto-injector from light. Store auto-injector in its box.

Makena single- and multi-dose vials (for intramuscular injection)

Makena (NDC 64011-247-02) is supplied as 1 mL of a sterile preservative-free clear yellow solution in a single-dose glass vial.

Each 1 mL vial contains hydroxyprogesterone caproate USP, 250 mg/mL (25% w/v), in castor oil USP (30.6% v/v) and benzyl benzoate USP (46% v/v).

Single unit carton: Contains one 1 mL single-dose vial of Makena containing 250 mg of hydroxyprogesterone caproate.

Makena (NDC 64011-243-01) is supplied as 5 mL of a sterile clear yellow solution in a multi-dose glass vial.

Each 5 mL vial contains hydroxyprogesterone caproate USP, 250 mg/mL (25% w/v), in castor oil USP (28.6% v/v) and benzyl benzoate USP (46% v/v) with the preservative benzyl alcohol NF (2% v/v).

Single unit carton: Contains one 5 mL multi-dose vial of Makena (250 mg/mL) containing 1250 mg of hydroxyprogesterone caproate.

Store at 20° to 25°C (68° to 77°F). Do not refrigerate or freeze.

Use multi-dose vials within 5 weeks after first use.

Caution: Protect vial from light. Store vial in its box. Store upright.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Counsel patients that Makena injections may cause pain, soreness, swelling, itching or bruising. Inform the patient to contact her physician if she notices increased discomfort over time, oozing of blood or fluid, or inflammatory reactions at the injection site [*see Adverse Reactions (6.1)*].

Distributed by: AMAG Pharmaceuticals, Inc.
Waltham, MA 02451

02/2018

PATIENT INFORMATION
MAKENA (mah-KEE-na)
(hydroxyprogesterone caproate injection)
auto-injector for subcutaneous use
MAKENA (mah-KEE-na)
(hydroxyprogesterone caproate injection)
vial for intramuscular use

Read this Patient Information leaflet before you receive MAKENA. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is MAKENA?

MAKENA is a prescription hormone medicine (progestin) used in women who are pregnant and who have delivered a baby too early (preterm) in the past. MAKENA is used in these women to help lower the risk of having a preterm baby again. It is not known if MAKENA reduces the number of babies who are born with serious medical conditions or die shortly after birth. MAKENA is for women who:

- Are pregnant with one baby.
- Have had a preterm delivery of one baby in the past.

MAKENA is not intended for use to stop active preterm labor.
It is not known if MAKENA is safe and effective in women who have other risk factors for preterm birth.
MAKENA is not for use in women under 16 years of age.

Who should not receive MAKENA?

MAKENA should not be used if you have:

- blood clots or other blood clotting problems now **or** in the past
- breast cancer or other hormone-sensitive cancers now **or** in the past
- unusual vaginal bleeding not related to your current pregnancy
- yellowing of your skin due to liver problems during your pregnancy
- liver problems, including liver tumors
- high blood pressure that is not controlled

What should I tell my healthcare provider before receiving MAKENA?

Before you receive MAKENA, tell your healthcare provider about all of your medical conditions, including if you have:

- a history of allergic reaction to hydroxyprogesterone caproate, castor oil, or any of the other ingredients in MAKENA. See the end of this Patient Information leaflet for a complete list of ingredients in MAKENA.
- diabetes or pre-diabetes.
- epilepsy (seizures).
- migraine headaches.
- asthma.
- heart problems.
- kidney problems.
- depression.
- high blood pressure.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
MAKENA may affect the way other medicines work, and other medicines may affect how MAKENA works.
Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I receive MAKENA?

- **Do not** give yourself MAKENA injections. A healthcare provider will give you the MAKENA injection 1 time each week (every 7 days) either:
  - in the back of your upper arm as an injection under the skin (subcutaneous), **or**
  - in the upper outer area of the buttocks as an injection into the muscle (intramuscular).
- You will start receiving MAKENA injections anytime from 16 weeks and 0 days of your pregnancy, up to 20 weeks and 6 days of your pregnancy.
- You will continue to receive MAKENA injections 1 time each week until week 37 (through 36 weeks and 6 days) of your pregnancy or when your baby is delivered, whichever comes first.

What are the possible side effects of MAKENA?

MAKENA may cause serious side effects, including:

- **Blood clots**. Symptoms of a blood clot may include:
  - leg swelling
  - redness in your leg
  - a spot on your leg that is warm to the touch
  - leg pain that gets worse when you bend your foot

  Call your healthcare provider right away if you get any of the symptoms above during treatment with MAKENA.
- **Allergic reactions**. Symptoms of an allergic reaction may include:
  - hives
  - itching
  - swelling of the face

  Call your healthcare provider right away if you get any of the symptoms above during treatment with MAKENA.
- **Decrease in glucose (blood sugar) tolerance**. Your healthcare provider will need to monitor your blood sugar while taking MAKENA if you have diabetes or pre-diabetes.
- **Your body may hold too much fluid (fluid retention)**.
- **Depression**.
- **Yellowing of your skin and the whites of your eyes (jaundice)**.
- **High blood pressure**.

The most common side effects of MAKENA include:

- pain, swelling, itching or a hard bump at the injection site
- hives
- itching
- nausea
- diarrhea

Call your healthcare provider if you have the following at your injection site:

- increased pain over time
- oozing of blood or fluid
- swelling

Other side effects that may happen more often in women who receive MAKENA include:

- Miscarriage (pregnancy loss before 20 weeks of pregnancy)
- Stillbirth (fetal death occurring during or after the 20th week of pregnancy)
- Hospital admission for preterm labor
- Preeclampsia (high blood pressure and too much protein in your urine)
- Gestational hypertension (high blood pressure caused by pregnancy)
- Gestational diabetes
- Oligohydramnios (low amniotic fluid levels)

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of MAKENA. For more information, ask your healthcare provider or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store MAKENA?

- **MAKENA auto-injector for subcutaneous use**:
  - Store the auto-injector at room temperature between 68°F to 77°F (20°C to 25°C).
  - Do not refrigerate or freeze.
  - Protect the auto-injector from light.
  - Store the auto-injector in its box.
- **MAKENA vial for intramuscular use**:
  - Store the vial at room temperature between 68°F to 77°F (20°C to 25°C).
  - Do not refrigerate or freeze.
  - Protect the vial from light.
  - Store the vial in its box in an upright position.

Keep MAKENA and all medicines out of the reach of children.

General information about the safe and effective use of MAKENA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use MAKENA for a condition for which it was not prescribed. Do not give MAKENA to other people, even if they have the same symptoms you have. It may harm them.
This leaflet summarizes the most important information about MAKENA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about MAKENA that is written for health professionals.

What are the ingredients in MAKENA?

Active ingredient: hydroxyprogesterone caproate
Inactive ingredients: castor oil and benzyl benzoate. 5 mL multi-dose vials also contain benzyl alcohol (a preservative).

Distributed by: AMAG Pharmaceuticals, Inc.

For more information, go to www.MAKENA.com or call AMAG Pharmaceuticals Customer Service at the toll-free number 1-877-411-2510.

This Patient Information has been approved by the U.S. Food and Drug Administration Revised: 02/2018

EXHIBIT B

FDA Briefing Document
NDA 021945
Hydroxyprogesterone Caproate Injection
(trade name Makena)

Bone, Reproductive, and Urologic Drugs Advisory Committee (BRUDAC) Meeting
October 29, 2019
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Office of New Drugs

Division of Biometrics III
Division of Biometrics VII
Office of Biostatistics
Office of Translational Sciences

Division of Epidemiology II
Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought new information from the new drug application for Makena (17-hydroxyprogesterone caproate) to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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INTRODUCTORY MEMORANDUM

To: Bone, Reproductive and Urologic Drugs Advisory Committee

From: Christine P. Nguyen, MD
Deputy Director for Safety

Hylton V. Joffe, MD, MMSc
Director

Division of Bone, Reproductive, and Urologic Products (DBRUP)

Subject: Makena (hydroxyprogesterone caproate injection)
New Drug Application 021945/Supplement 023
Overview of topics to be discussed at the October 29, 2019, advisory committee meeting

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The FDA is convening this Advisory Committee (AC) meeting to discuss the evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth and improving neonatal outcomes to inform FDA's regulatory decision-making for this product. In 2011, Makena received accelerated approval (a type of approval discussed in greater detail below) based on a reduced risk of recurrent preterm birth (PTB) prior to 37 weeks, a surrogate endpoint that FDA considered reasonably likely to predict clinical benefit to the neonate. Consistent with FDA's accelerated approval framework [21 CFR part 314, subpart H and section 506(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)], FDA required the Applicant to conduct a post-approval confirmatory trial to verify and describe the clinical benefit. Completed at the end of 2018, this confirmatory trial did not verify Makena's efficacy on obstetrical or neonatal outcomes. In a supplemental new drug application (sNDA), the Applicant proposes to add findings from this trial to the drug label.

BACKGROUND:

Current clinical practice

Preterm birth, defined as birth prior to 37 weeks of gestation, currently affects approximately 10% of all births and 8% of singleton pregnancies.[1] Premature birth is a significant public health problem because these infants are at an increased risk of neonatal mortality and significant morbidity, as well as long-term physical and developmental impairment. To date, there are no drugs approved for reducing neonatal morbidity or mortality or long-term sequelae of preterm birth.

Progesterone, administered by intramuscular injection or intravaginally, has been used for certain conditions that may increase a pregnant woman's risk of PTB. Current professional practice

[1] https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm (accessed September 19, 2019)

guidelines recommend progesterone treatment starting in the second trimester of pregnancy to reduce the risk of recurrent preterm birth in women with a singleton pregnancy and a prior spontaneous preterm birth (sPTB). The guidelines also recommend vaginal progesterone to reduce the risk of PTB in women without a prior preterm birth and with a shortened cervix in the current pregnancy, although such use is not FDA-approved.[2] Makena is the only pharmacotherapy approved to reduce the risk of recurrent preterm birth. Based on its accelerated approval, Makena's indication states that it is approved to "reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. The effectiveness of Makena is based on improvement in the proportion of women who delivered <37 weeks of gestation. There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity."

Regulatory History of Hydroxyprogesterone Caproate:
The drug substance of Makena, hydroxyprogesterone caproate (HPC), also referred to as 17-HPC, 17-OHPC, or 17P, was approved by FDA in 1956 for conditions generally responding to progestogens, under the tradename Delalutin (HPC) injection 125 mg/mL and 250 mg/ml (NDAs 010347, 016911). This approval was based on safety considerations because it occurred prior to the Kefauver-Harris Amendment of 1962 to the FD&C Act requiring that approved drugs be supported by substantial evidence of effectiveness, in addition to demonstrated safety. Delalutin remained approved for certain gynecologic indications after undergoing the Drug Efficacy Study Implementation review, which determined the efficacy of marketed drugs approved before 1962. At the Applicant's request, FDA withdrew approval of the NDAs for Delalutin in 2000 (not for efficacy or safety reasons) (65 Fed. Reg. 55264, Sept. 13, 2000). FDA has approved generic products of Delalutin that are currently marketed. Note that Delalutin and its generics are not approved for reducing the risk of preterm birth.

Published literature from the 1960s through the 1980s included several clinical studies evaluating the efficacy of HPC for obstetrical uses. Conflicting findings regarding the effectiveness of HPC for the prevention of PTB prompted the National Institute for Child Health and Human Development (NICHD), via the Maternal-Fetal Medicine Units (MFMU) Network, to conduct a multicenter, double-blind, placebo-controlled clinical trial in women with a history of spontaneous preterm singleton birth to assess the efficacy of HPC for preventing recurrent PTB (Study 17P-CT-002, or Trial 002 hereinafter). In June 2003, the trial's findings were published,[3] reporting that HPC 250 mg injection reduced the proportion of women who delivered at less than 37 weeks gestation.

[2] American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin: Prediction and Prevention of Preterm Birth (2012, reaffirmed 2018); Society for Maternal-Fetal Medicine Statement: "The choice of progestogen for the prevention of preterm birth in women with singleton pregnancy and prior preterm birth" (March 2017). While the ACOG Practice Bulletin did not specify the formulation of progesterone for women with a prior sPTB, SMFM recommended treatment with hydroxyprogesterone caproate injection and not vaginal progesterone in this population.

[3] Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med. 2003;348(24):2379-85.

Makena's accelerated approval

In 2006, an applicant submitted NDA 021945 seeking marketing approval of HPC injection for the prevention of recurrent PTB. The NDA relied on data from the MFMU Network Trial 002 for primary support of efficacy and safety. At that time, no drug was approved in the U.S. to reduce the risk of PTB. However, HPC was compounded and used widely for the prevention of PTB in women at high risk.

After three review cycles and one Advisory Committee meeting, in February 2011, the FDA granted Makena accelerated approval based on reduction in preterm birth prior to 37 weeks, a surrogate endpoint considered to be reasonably likely to predict the clinical benefit of reducing neonatal morbidity or mortality.

Initiated in 1999 and completed in 2002, Trial 002 enrolled 463 women with a singleton pregnancy and at least one prior sPTB from 19 university-based clinical centers in the United States in the MFMU Network. The primary efficacy endpoint was the proportion of pregnant women delivering prior to 37 weeks gestation, with those delivering prior to 35 or 32 weeks as secondary endpoints. The trial showed that Makena (HPC 250 mg) injection administered intramuscularly once weekly starting at 16 weeks 0 days (16^0) to 20 weeks 6 days (20^6) gestation and used through 36^6 weeks gestation or birth reduced the proportion of women who delivered <37 weeks gestation from 55% (placebo) to 37% (Makena). The treatment difference was -17.8% [95% confidence interval (CI): -28%, -7.4%]. This treatment benefit appeared independent of race, number of prior preterm deliveries, and gestational age of the prior preterm birth. The treatment effect was sufficiently persuasive to support drug approval based on the findings of a single adequate and well-controlled trial. The proportions of women delivering at <35 and <32 weeks gestation were also statistically lower among women treated with Makena compared to placebo. The treatment difference was -9.4% (95% CI: -19.0%, -0.4%) for delivery <35 weeks gestation and -7.7% (95% CI: -16.1%, -0.3%) for delivery <32 weeks gestation.

Issues regarding generalizability of Trial 002's findings to the broader U.S. population included (a) approximately 60% of the trial participants being self-identified Blacks, (b) subject recruitment from only academic centers, with 25% of subjects from a single academic center, and (c) the notably high rate of recurrent preterm birth in the placebo arm (55%).[4] As a condition of accelerated approval, the Applicant was required to submit data from a confirmatory efficacy and safety trial to verify the clinical benefits of Makena, and the trial was to be completed with due diligence.

CONFIRMATORY TRIAL (Trial 003)

Prior to approving Makena in 2011, the FDA recognized the challenges of the feasibility of conducting a confirmatory efficacy and safety trial in the United States, given the endorsement of professional practice guidelines and accepted clinical practice of using progesterone for preterm birth. Prior to approval, the FDA required that the Applicant provide evidence that it could successfully complete the confirmatory trial, which must be ongoing at the time of approval, and that at least 10% of subjects be enrolled from the U.S. and Canada. Initiated in 2009 and completed in 2018, this confirmatory trial (Trial 003) was a multicenter, international,

[4] Background recurrent preterm birth rate used to power Trial 002 was 36%, as this was the background rate from the MFMUN uterine monitoring trial in the 1990s.

randomized, double-blind, placebo-controlled study that enrolled women with eligibility criteria like those of Trial 002. The trial's coprimary efficacy endpoints were delivery prior to 35 weeks gestation and a neonatal morbidity/mortality composite index (neonatal composite index).[5] The inclusion of a clinical endpoint (the neonatal composite index) addressed the accelerated approval's regulations of verifying that initial findings based on a surrogate endpoint (gestational age at delivery) lead to direct clinical benefit. Trial 003 randomized a total of 1,708 women from nine countries, with Russia, Ukraine, and the United States enrolling 36%, 25%, and 23% of women, respectively. Data were available for 1651 liveborn neonates. The trial did not demonstrate a statistically significant treatment effect for the coprimary endpoints of proportion of women delivering prior to 35 weeks (11% Makena compared to 12% placebo, p=0.72) or neonatal composite index (5.4% Makena compared to 5.2% placebo, p=0.84). Also, no differences between Makena and placebo were seen in the secondary outcomes related to other gestational ages at delivery (<37 weeks [23% Makena vs. 22% placebo, p=0.57), <32 weeks gestation [4.8% Makena vs. 5.2% placebo, p=0.70]) or for the individual components of the neonatal index.

The Applicant raised concerns that the study populations of Trial 002 (U.S only) and Trial 003 (international, including U.S.) differed substantially and that this may have contributed to the discordant outcomes between the two trials. Therefore, exploratory subgroup analyses and comparisons of Trial 003's U.S. population (003-U.S. subgroup) and non-U.S. patients were undertaken. There were no relevant differences in the treatment effect when analyzed by region (U.S. vs. non-U.S.), even though the non-U.S. subgroup appeared to have a lower risk profile based on demographics, social, and behavioral factors compared to the U.S. subgroup. There was no evidence of interaction between treatment and U.S. vs. non-U.S. region for the coprimary endpoints. In the 003-U.S. subgroup:

- Makena did not improve the neonatal composite index. The treatment effect was -2.2% (95% CI: -8.3, 3.9) when analyzed using the stratified Cochran-Mantel-Haenszel (CMH) method and -0.2% (95% CI: -4.9, 2.8) using another approach known as shrinkage analysis.
- Makena did not reduce the risk of delivery <35 weeks (16% Makena vs. 18% placebo). The treatment difference was -2.2% (95% CI: -10.1, 5.7) using the stratified CMH analytical method; this difference was -0.8% (95% CI: -6.0, 3.5) with shrinkage estimation.
- Point estimates of the proportions of women with delivery occurring <37 weeks (33% Makena vs. 28% placebo, a treatment effect of 4.7% [95% CI: -5%, 14%] by the CMH method) or <32 weeks (5.5% Makena vs. 9.2% placebo, a treatment effect of -3.9% [95% CI: -9.6, 1.7] by the CMH method) showed contradictory trends in the treatment effect.

A comparison among Trial 003 overall, the 003-U.S. subgroup, and Trial 002 populations indicated that a greater proportion of subjects in Trial 002 had certain risk factors for PTB, such as being self-identified Blacks or having > 1 prior sPTB, than the 003-U.S. subgroup or Trial 003 overall. However, exploratory subgroup analyses did not show statistically significant

[5] The neonatal morbidity/mortality composite index includes neonatal death, Grade 3 or 4 intraventricular hemorrhage, respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, and proven sepsis.

interactions between these risk factors and treatment effect of Makena in Trial 002 or Trial 003. Although these risk factors may have an impact on the PTB rate, there was no evidence in Trial 003 that they impact the treatment effect nor was there consistent convincing evidence of treatment benefit within a specific subpopulation across the two trials.

Published literature on progesterone's effect on preterm birth in women with a prior sPTB
Because findings from Trial 003 were discordant with those of Trial 002, we evaluated published evidence from six randomized, placebo-controlled trials that assessed the effect of progesterone in preterm birth and that included pregnant women with a prior sPTB. These trials studied vaginal progesterone at different doses (90 – 200 mg) in women with various risks for PTB, including a history of sPTB, with different gestational ages at delivery as the primary outcome. The overall evidence based on subgroup analyses in pregnant women with a prior sPTB did not suggest a treatment benefit with progesterone over placebo in reducing the risk of recurrent PTB in these women. These trials and their findings, however, are not directly applicable to Makena; none evaluated injectable HPC in the same target population measuring the same efficacy endpoints as Makena. We also reviewed two recent large meta-analyses. These meta-analyses evaluated progesterone formulations, doses, patient populations, and endpoints dissimilar to those of the trials for Makena and did not reliably inform the treatment effect of Makena for its intended use.

Accelerated approval and evidentiary standards for drug approval
When appropriate, the accelerated approval pathway allows for earlier approval of a drug to treat a serious condition and fill an unmet medical need based on a surrogate endpoint that is reasonably likely to predict clinical benefit but is not itself a direct measure of clinical benefit. The Applicant is required to conduct trial(s) after receiving accelerated approval to confirm the expected clinical benefit. If the confirmatory trial(s) shows that the drug provides clinical benefit, then the conditions initially attached to accelerated approval are generally terminated. (See 21 CFR 314.560.) If the confirmatory trial(s) fail to demonstrate such benefit, FDA may withdraw approval of the drug in accordance with section 506(c)(3) of the FD&C Act and 21 CFR 314.530. With accelerated approval, there is less certainty at the time of approval that the drug will ultimately be shown to improve how patients feel, function or survive; however, this pathway provides earlier patient access than would otherwise be possible to an approved drug that is reasonably likely to confer clinical benefit for a serious condition with an unmet need. In the case of Makena, FDA granted accelerated approval based on the reduction in preterm birth seen in Trial 002; however, confirmatory Trial 003 did not verify clinical benefit on adverse neonatal outcomes to infants born prematurely.

For FDA approval, including accelerated approval, the drug must meet the regulatory standard of "substantial evidence" of effectiveness and the benefits must outweigh the risks. Generally, FDA interprets substantial evidence of effectiveness as evidence of effectiveness from two or more adequate and well-controlled trials. A single positive trial, even if well-designed and well-conducted, may have undetected systemic biases or may reflect a chance finding, increasing the risk of concluding that a drug is effective when in fact it is not. The requirement for at least two adequate and well-controlled trials ensures independent substantiation of experimental findings and strengthens a conclusion of effectiveness. Nonetheless, when appropriate, FDA has the authority and flexibility to conclude that there is substantial evidence of effectiveness based on a

single adequate and well-controlled trial. In the case of Makena, FDA determined that Trial 002 was adequate, well-controlled and very persuasive and concluded that this single trial provided substantial evidence of an effect on a surrogate endpoint (effectiveness for reduction in the risk of recurrent preterm birth). It is important to note, however, that at the time this determination was made in 2011, there were no other adequate and well-controlled trials with Makena, and that had there been such additional trial(s), FDA would have considered those data when deciding whether there was substantial evidence of effectiveness.

There are two important scientific and regulatory implications for Makena:

- Accelerated approval: A drug approved under the accelerated approval pathway based on a surrogate endpoint reasonably likely to predict clinical benefit must undergo a confirmatory trial postapproval to verify clinical benefit (i.e., an improvement in how patients feel, function or survive). In the case of Makena, confirmatory Trial 003 did not demonstrate a reduction in adverse neonatal outcomes from preterm birth; therefore, the clinical benefit of Makena remains unverified.

- Substantial evidence of effectiveness: Trial 003 also did not confirm an effect of Makena on gestational age of delivery, the surrogate endpoint used in Trial 002 to support accelerated approval. This raises the question as to whether Makena's accelerated approval is still supported by substantial evidence of effectiveness for the reduction in recurrent preterm birth.

AREAS OF FOCUS FOR ADVISORY COMMITTEE

Based on the above considerations, the key issues are whether there remains substantial evidence of effectiveness of Makena on preterm birth, the unconfirmed clinical benefit of Makena on neonatal outcomes, and implications for Makena's marketing status. Makena received accelerated approval based on findings from Trial 002, which showed a reduction in the proportion of women with preterm delivery <37 weeks compared to placebo, a surrogate endpoint considered reasonably likely to predict clinical benefit. However, Trial 003, an adequate and well-controlled, well-conducted and appropriately powered confirmatory trial, did not show a reduction in preterm birth with Makena compared to placebo, nor did it demonstrate a reduction in neonatal morbidity/mortality. Under accelerated approval regulations, FDA may withdraw the approval of Makena if the Applicant fails to provide confirmatory evidence of efficacy and safety. To place this discussion in the appropriate context, we ask that the Advisory Committee members consider:

- The applicability of the findings of Trial 003 to the U.S. population
- Factors, if any, that may account for the differences in outcomes between Trial 002 and Trial 003
- Whether there continues to be substantial evidence that Makena reduces the risk of recurrent preterm birth in the context of two adequate and well-controlled trials with discrepant efficacy findings on this surrogate endpoint
- If a new confirmatory trial is required, the design of such a trial, including the comparator arm, dose(s) of study medication, location (U.S./North America or international), efficacy endpoints and importantly, the feasibility and likelihood of successfully completing such a trial in a timely manner

- If Makena were to be withdrawn from the market because of lack of efficacy, the likely consequences and their potential impact on public health.

We look forward to a thorough and reasoned discussion of these complex, important matters. Thank you in advance for the vital public health contribution you are making through your participation in this meeting.

Draft Points to Consider:

1. Discuss the effectiveness of Makena, including:
    a. The effects of Makena on recurrent preterm birth in Trial 003, and your interpretation of the discrepant preterm birth results between Trial 002 and Trial 003;
    b. The effects of Makena on neonatal morbidity and mortality;
    c. Relevance of the findings in Trial 003 to the U.S. population and current clinical practice.

2. If a new efficacy trial were to be conducted, discuss the study design, including control, dose(s) of study medication, efficacy endpoints and the feasibility of completing such a trial.

3. Discuss the potential consequences of withdrawing Makena on patients and clinical practice.

4. Do the findings from Trial 003 verify the clinical benefit of Makena on neonatal outcomes?

    Provide rationale for your vote.

5. Based on the findings from Trial 002 and Trial 003, is there substantial evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth?

    Provide rationale for your vote.

6. FDA approval, including accelerated approval, of a drug requires substantial evidence of effectiveness, which is generally interpreted as clinically and statistically significant findings from two adequate and well-controlled trials, and sometimes from a single adequate and well-controlled trial. For drugs approved under the accelerated approval pathway based on a surrogate endpoint, the Applicant is required to conduct adequate and well-controlled postapproval trial(s) to verify clinical benefit. If the Applicant fails to conduct such postapproval trial(s) or if such trial(s) do not verify clinical benefit, FDA may, following an opportunity for a hearing, withdraw approval.

    Should FDA:

    A. Pursue withdrawal of approval for Makena
    B. Leave Makena on the market under accelerated approval and require a new confirmatory trial
    C. Leave Makena on the market without requiring a new confirmatory trial

    Provide rationale for your vote and discuss the following:

    - Vote (A) (withdraw approval) may be appropriate if you believe the totality of evidence does not support Makena's effectiveness for its intended use.

- Discuss the consequences of Makena removal (if not previously discussed in Discussion point 3)

- Vote (B) (require a new confirmatory trial) may be appropriate if you believe the totality of evidence supports Makena's effectiveness in reducing the risk of recurrent preterm birth, but that there is no substantial evidence of effectiveness on neonatal outcomes. Vote (B) would also reflect a belief that a new confirmatory trial is necessary and feasible.

    - Discuss how the existing data provide substantial evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth, based on the surrogate endpoint of gestational age at delivery.

    - Also discuss key study elements, including study population, control, dose(s), and efficacy endpoints of the new confirmatory trial (if not previously discussed in Discussion point 2) and approaches to ensure successful completion of such a trial.

- Vote (C) (leave Makena on the market without a new confirmatory trial) may be appropriate if you believe Makena is effective for reducing the risk of recurrent preterm birth and that it is not necessary to verify Makena's clinical benefit in neonates.

    - Discuss how the existing data provide substantial evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth and why it is not necessary to verify Makena's clinical benefits in neonates.

1. Background

1.1. The Condition and Treatment Options

1.1.1. Preterm Birth

Preterm birth (PTB), defined as delivery between 20 and 37 completed weeks of gestation, is a significant public health concern. Preterm birth may be spontaneous (birth following a spontaneous process, such as preterm labor or preterm premature rupture of membranes) or indicated (delivery initiated by the healthcare provider for maternal or fetal health). According to the Centers for Disease Control and Prevention, in 2017, the U.S. PTB rate was 9.9% overall and 8.1% in singleton pregnancies; the incidence was highest in black women (13.9%) compared to white or Hispanic women (9.1% and 9.6%, respectively).[6] The CDC reported that the rate of preterm birth in the U.S. declined from 2007 (10.4%) to 2014 (9.6%), mostly because of a decline in teenage pregnancy, but has increased from 2014 until 2017 (9.9%). The latter trend is mostly due to an increase in the rate of late preterm birth (delivery 34-36 weeks gestation), while rates for early preterm birth (less 34 weeks) have remained unchanged from 2015. The World Health Organization estimates the global PTB rate to be 10.6%, which is similar to the rate of 11.2% in North America, but there are differences across geographic regions, ranging from 8.7% in Europe to 13.4% in North Africa.[7] In 2015, PTB accounted for 17% of infant deaths [8] and surviving children often suffer developmental delay or long-term neurologic impairment. In 2016, complications of PTB were the leading cause of death globally in children younger than 5 years of age, accounting for approximately 16% of all deaths in this age group, and 35% of deaths among neonates.[9] In general, the risk of adverse outcomes in the preterm neonate decreases with increasing gestational age at delivery.

While the burden of PTB is clear, the causes of PTB are less so, and identifying women who will give birth preterm is challenging. Spontaneous PTB represents a syndrome and its causes are multifactorial. Risk factors for PTB include uterine distension (seen in multifetal pregnancies and polyhydramnios), dysfunction of the cervix (reduced mechanical competence, either resulting from genetic mutations in components of collagen that is required for integrity of the cervix or from repeated surgeries on the cervix), infection of the lower genital tract, and other factors (such as cigarette smoking, inadequate maternal weight, and illicit drug use). The contribution of these factors to PTB, however, is not well-characterized. However, an accepted major risk factor is short cervical length (typically defined as <25 mm observed prior to 24 weeks gestation). Regarding the risk of recurrent PTB, one of the strongest risk factors is a history of a preterm birth, which increases the risk of PTB by about 1.5 to 2-fold. Additionally, the number of prior PTBs and the gestational age of the prior PTBs impact the recurrence risk.

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[6] National Vital Statistics Reports, Vol 67, No. 8, November 7, 2018. https://www.cdc.gov/nchs/data/nvsr/nvsr67/nvsr67_08-508.pdf

[7] Chawanpaiboon S, Vogel JP, Moller A-B, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systemic review and modelling analysis. Lancet Glob Health 2019;7(1): e37-46.

[8] CDC – Division of Reproductive Health, National center for Chronic Disease Prevention and Health Promotion. https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm

[9] UN Inter-Agency Group for Child Mortality Estimation. Levels and trends in child mortality: Report 2017. New York: United Nations Children's Fund, 2017.

Nonetheless, two-thirds of PTBs occur among women with no identifiable risk factors, causality of PTB has been difficult to determine, and the pathogenesis remains poorly understood.[10]

1.1.2. Treatment to Reduce the Risk of Recurrent Preterm Birth

In January 2003, Trial 002 was presented by the NICHD as the first abstract at the Society for Maternal-Fetal Medicine Meeting. The positive findings from this trial immediately gained extensive media attention, leading to the wide use of compounded HPC to reduce the risk of recurrent PTB. Following the June 2003 publication of Trial 002 in the New England Journal of Medicine, the American College of Obstetricians and Gynecologists (ACOG) Committee on Obstetric Practice endorsed the use of progesterone only in women with a documented history of a previous spontaneous birth at less than 37 weeks of gestation. In its most recent Practice Bulletin (published 2012, reaffirmed 2018), ACOG recommends progesterone (without specifying the formulation of progesterone) starting in the second trimester in women with a singleton pregnancy and a prior sPTB. ACOG also recommends vaginal progesterone in women with a singleton pregnancy with a shortened cervix and without a prior sPTB. In 2003, the Society for Maternal-Fetal Medicine (SMFM) recommended treatment with either HPC injection or vaginal progesterone for women with a prior spontaneous PTB to prevent the recurrence of PTB; this recommendation was reaffirmed in 2008.[11] Based on published findings of several clinical trials, the SMFM in 2012 revised the guideline to recommend that HPC 250 mg IM weekly be given, starting at 16 to 20 weeks of gestation until 36 weeks or birth, to women with a singleton gestation whose prior sPTB occurred between 20-36$^{6/7}$ weeks gestation.[12] In 2017, SMFM reaffirmed its 2012 recommendation and added that vaginal progesterone should not be considered a substitute for HPC in these patients.[13] As noted previously, Makena is the only FDA-approved treatment for PTB.

1.2. Regulatory Background

1.2.1. Regulatory Standards of Drug Approval

1.2.1.1. Accelerated Approval

Under the accelerated approval pathway [21 CFR part 314, subpart H, and 506(c) of the FD&C Act], FDA may grant marketing approval for a new drug based on adequate and well-controlled clinical trials establishing that the drug has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict

[10] PRETERM BIRTH CAUSES, CONSEQUENCES, AND PREVENTION. Committee on Understanding Premature Birth and Assuring Healthy Outcomes. Board on Health Sciences Policy. Richard E. Behrman and Adrienne Stith Butler, Editors. INSTITUTE OF MEDICINE OF THE ACADEMIES. THE NATIONAL ACADEMIES PRESS. Washington, D.C. Copyright 2007 by the National Academy of Sciences.

[11] Society for Maternal-Fetal Medicine Publications Committee: Use of progesterone to reduce preterm birth. ACOG Committee opinion number 419, October 2008 (replaces no. 291, November 2003) Obstet Gynecol, 112 (2008), pp. 963-965.

[12] Society for Maternal-Fetal Medicine Publications Committee, with assistance of Vincenzo Berghella. Progesterone and preterm birth prevention: translating clinical trials data into clinical practice. Am J Obstet Gynecol, 206 (2012), pp. 376-386.

[13] The choice of progestogen for the prevention of preterm birth in women with singleton pregnancy and prior preterm birth Society for Maternal-Fetal Medicine (SMFM) Publications Committee, 2017

clinical benefit. A measurement of clinical benefit directly assesses how a patient feels, functions, or survives. Because gestational age at delivery does not directly measure how a neonate feels, functions, or survives, it is considered a surrogate endpoint, but one that we determined to be a reasonably reliable predictor of the clinical benefit for the neonate. In general, two major concerns with surrogate endpoints are (1) it may not be a true predictor of the clinical benefit and (2) it may not provide a quantitative measure of benefit. Thus, approval under this regulation requires that the Applicant study the drug further to verify and describe its clinical benefit. The confirmatory trials must be adequate and well-controlled and be conducted with due diligence. These trials are usually already ongoing at the time of accelerated approval to ensure their timely completion.

For drugs approved under the accelerated approval pathway, the regulations also outline the conditions that may prompt FDA to withdraw approval:

(1) A postmarketing clinical study fails to verify clinical benefit;
(2) The Applicant fails to perform the required postmarketing study with due diligence;
(3) Use after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the drug product;
(4) The Applicant fails to adhere to the postmarketing restrictions agreed upon;
(5) The promotional materials are false or misleading; or
(6) Other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.
(See 21 CFR 314.530)

1.2.1.2. Substantial Evidence of Effectiveness

For FDA approval, including accelerated approval, a drug must meet the regulatory standard of "substantial evidence" of effectiveness for the intended use and the benefits must outweigh the risks.[14] Traditionally, FDA has interpreted substantial evidence of effectiveness as clinically and statistically significant findings from at least two adequate and well-controlled trials. A single positive trial, even if well-conducted, may have biases or may reflect a chance finding, increasing the risk of concluding that a drug is effective when in fact it is not. The requirement for at least two adequate and well-controlled trials ensures independent substantiation of experimental findings and strengthens a conclusion of effectiveness. Nonetheless, when appropriate, FDA has the authority and flexibility to conclude that there is substantial evidence of effectiveness based on a single adequate and well-controlled trial. Conclusions based on two high-quality trials will generally be more secure than those based on a single comparably persuasive study. Therefore, reliance on a single trial is generally limited to situations where a second trial is not feasible (e.g., rare diseases) or ethical (e.g., when one trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a serious disease). Characteristics of a single trial that could support a conclusion of substantial evidence of effectiveness include a large multicenter trial with consistency across study subsets, multiple studies within a single study, multiple endpoints involving different events, and statistically very persuasive findings.

[14] FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products, May 1998.

1.3. Trial 002 and Approval of Makena

1.3.1. Trial 002

In 1999, the National Institute of Child Health and Human Development initiated a multicenter, double-blind, randomized, placebo-controlled clinical trial through its Maternal-Fetal Medicine Units Network to evaluate the efficacy and safety of HPC injection. The study randomized pregnant women with at least one documented prior sPTB of a singleton fetus to either HPC or placebo in a 2:1 ratio. Eligible subjects were at a gestational age between 16^0 weeks and 20^6 weeks at randomization. Pregnancies with multifetal gestation and known major fetal anomaly (as documented by an ultrasound examination after 14 weeks gestation) were excluded. Women who had progesterone treatment prior to randomization were also excluded, as were women experiencing maternal medical complications (e.g., hypertension requiring medication, seizure disorder) or obstetrical complications. The subjects received HPC 250 mg weekly injections or placebo vehicle beginning on the day of randomization through 36^6 weeks gestation or delivery, whichever occurred first. The primary efficacy endpoint was the proportion of delivery prior to 37^0 weeks gestation in the intent-to-treat (ITT) population.

A total of 463 women were randomized to receive either HPC (N=310) or placebo (N= 153). The two study groups were similar with respect to age, race or ethnicity, body mass index prior to pregnancy, marital status, education, and substance use during pregnancy; 59% of the subjects were African American. Of the 463 women randomized, 418 (90.3%) completed dosing through 36^6 weeks or birth, including 279 (90.0%) in the HPC group and 139 (90.8%) in the placebo group. The efficacy results for gestational age at delivery are shown in Table 1.

Table 1: Proportion of Subjects in Each Treatment Arm Who Delivered at <37 Weeks, <35 Weeks, and <32 Weeks Gestational Age (Trial 002)

Delivery outcome	HPC* %	Placebo %	Treatment Difference and 95% Confidence Interval**
<37 weeks	37.1	54.9	-17.8% [-28.0%. -7.4%]
<35 weeks	21.3	30.7	-9.4% [-19.0%, -0.4%]
<32 weeks	11.9	19.6	-7.7% [-16.1%, -0.3%]

*Four HPC-treated subjects were lost to follow-up. They were counted as deliveries at their gestational ages at time of last contact (184, 220, 343, and 364 weeks).
**Adjusted for interim analysis.
Source: FDA-approved Makena prescribing information

Pregnancy after the time of randomization was maintained for an average of six days longer in the HPC group (131 vs. 125 days), with the mean gestational age at delivery being one week greater (36.2 vs. 35.2 weeks for HPC and placebo subjects, respectively).

Makena's effect on reducing recurrent preterm birth appeared independent of race, number of previous preterm deliveries, and gestational age of previous preterm birth. The proportion of women who delivered at <37 weeks in the placebo group appeared notably high (55%). See Table 2.

Table 2: Percentages of Subjects With Delivery <37 Weeks by Gestational Age of Previous Birth, Race, and Number of Previous Preterm Deliveries (Trial 002)

Characteristics	HPC n/N (%)	Placebo n/N (%)
Previous sPTB by gestational age		
20^0 - <28^0 weeks	32/82 (40.2%)	19/29 (65.5%)
28^0 - <32^0 weeks	21/66 (31.8%)	17/30 (56.7%)
32^0 - <35^0 weeks	30/84 (35.7%)	27/55 (49.1%)
35^0 - <37^0 weeks	31/78 (39.7%)	21/39 (53.8%)
Race		
Black	66/183 (36.1%)	47/90 (52.2%)
Non-black	49/127 (38.6%)	37/63 (58.7%)
Number of previous PTB		
1 prior PTB	74/224 (33.0%)	40/90 (44.4%)
2 prior PTB	27/56 (48.2%)	31/46 (67.4%)
≥3 prior PTB	14/30 (46.7%)	13/17 (76.5%)

Data based on ITT Population (all randomized subjects). The 4 subjects with missing outcome data were classified as having a preterm birth <37^0 weeks (i.e., treatment failure).
Abbreviations: n = number of subjects in a specific category who delivered study pregnancy at <37^0 weeks gestation; N = total number of subjects overall in a specific category
Source: Table 11-4, Final Report for Study 17-CT-002

This trial was terminated by the Data and Safety Monitoring Board prior to enrolling the planned 500 subjects because the pre-specified stopping criteria for the primary efficacy endpoint of delivery < 37 weeks gestation were attained at an interim analysis.

Data on the individual components that subsequently constituted the neonatal composite index were prospectively collected. The analysis of a composite index, developed by the Applicant at the request of the FDA, was conducted post-hoc, after the initial submission of the NDA in 2006, to evaluate adverse outcomes in live births and as supportive evidence of Makena's benefit on reducing the risk of recurrent preterm delivery. The neonatal composite index was based on the number of neonates who died or experienced respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), grade 3 or 4 intraventricular hemorrhage (IVH), proven sepsis, or necrotizing enterocolitis (NEC). Although the proportion of neonates who experienced one or more events was numerically lower in the Makena arm than placebo (12% vs. 17%, P=0.7), the number of adverse outcomes was limited and the difference between arms was not statistically significant. The same neonatal composite index was prospectively evaluated as a coprimary endpoint for Trial 003.

1.3.2. Approval of Makena

Following the publication of results from Trial 002 in 2003, Adeza Biomedical[15] obtained access to the NICHD data and began discussion with the FDA regarding submission of a new drug application (NDA) based on Trial 002.

[15] The NDA ownership was subsequently transferred to several entities, including Hologics, KV Pharmaceutical, Lumara Health, Inc., and AMAG. Hereafter, all are referred to as "the Applicant."

During the first review cycle of the NDA, FDA brought Makena to the Advisory Committee on Reproductive Health Drugs (the Committee) for discussion in August 2006. As noted previously, the primary endpoint of Trial 002 was the rate of PTB prior to 37 weeks gestation; however, 16 of 21 Committee members found that PTB <37 weeks was not an adequate surrogate for reduction in fetal/neonatal mortality and neonatal morbidity. Thirteen of the 21 Committee members voted that PTB <35 weeks was an adequate surrogate, and 12 members voted that the data submitted provided substantial evidence that Makena prevents PTB at <35 weeks. However, the Committee overwhelmingly voted (19 no, 2 yes) that the submitted data did not provide substantial evidence of benefit on neonatal mortality or morbidity, based on the results of the neonatal morbidity/mortality composite index.[16]

FDA did not approve the application in 2006.[17] The primary deficiency was that efficacy based on a single trial that relied on a surrogate endpoint (deemed by most Committee members to be an inadequate surrogate of neonatal morbidity and mortality) was not sufficiently robust to support approval. FDA determined that further study was needed to provide confirmatory evidence of the drug's efficacy in terms of direct clinical benefit on neonatal outcomes or through an established surrogate such as the rate of preterm birth prior to 35 and 32 weeks gestation. To address this deficiency, the FDA recommended that the Applicant submit a draft protocol and evidence of the feasibility of conducting an additional adequate and well-controlled trial to verify and describe further the clinical benefit of preventing recurrent PTB, as stated under the accelerated approval regulations.

In the second review cycle that began in 2008, the Applicant provided a protocol for a postapproval confirmatory trial for an accelerated approval, and another protocol for an infant follow-up study. During the review, the American College of Obstetricians and Gynecologists (ACOG) issued a revised Committee Opinion on Use of Progesterone to Reduce Preterm Birth.[18] In contrast to the 2003 Committee Opinion,[19] which stated:

> *"When progesterone is used, it is important to restrict its use to only women with a documented history of previous spontaneous birth at less than 37 weeks of gestation because unresolved issues remain, such as optimal route of drug delivery and long-term safety of the drug."*

The 2008 Committee Opinion stated:

> *"Progesterone supplementation for the prevention of recurrent preterm birth should be offered to women with a singleton pregnancy and a prior spontaneous preterm birth due to spontaneous preterm labor or premature rupture of membranes."*

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[16] Cross-Discipline Team Leader Review dated February 3, 2011. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000CrossR.pdf

[17] Approvable Letter, dated October 20, 2006.

[18] ACOG Committee on Obstetric Practice. Use of progesterone to reduce preterm birth. No. 419, October 2008.

[19] ACOG Committee on Obstetric Practice. Use of progesterone to reduce preterm birth. No. 291, November 2003.

FDA interpreted this new Opinion as establishing a *de facto* standard of care for women with a previous spontaneous PTB. FDA was concerned that this opinion could adversely impact recruitment of subjects into a placebo-controlled trial. Although the trial protocol (including study design, planned sample size, primary and secondary objectives, and proposed analysis plan) was deemed satisfactory, FDA declined to approve the application again in 2009, requesting that the Applicant provide adequate documentation that it would be feasible to conduct and successfully complete the confirmatory trial. FDA stated that "adequate assurance of feasibility of [the confirmatory trial] can only be addressed by actual initiation of the trial." Further, noting that one clinical site (University of Alabama at Birmingham) contributed 27% of the total number of subjects in Trial 002, FDA requested that the confirmatory trial include at least 15 investigational sites (US and non-US), with no single site enrolling more than 15% of the total number of subjects. Also, at least 10% of the total randomized subjects would need to be from US and Canadian sites.[20]

By the time of the third review cycle for Makena, multiple clinical studies evaluating the consequences of "late preterm birth" (births between 34^0 to 36^6 weeks gestation) had emerged to show that late-preterm infants are less physiologically and metabolically mature than term infants and are thus at higher risk of morbidity and mortality than term infants.[21,22,23,24] This new evidence led the FDA to determine that PTB < 37 weeks was an acceptable surrogate endpoint that is reasonably likely to predict clinical benefit. This determination also led the FDA to reconsider data from Trial 002. For the endpoint of delivery at < 37 weeks, the results were deemed compelling (with a sizeable treatment difference between groups and a p value of 0.0004) and not driven by data obtained from the University of Alabama at Birmingham alone. FDA concluded that evidence in Trial 002 was sufficient to support Makena improving the proportion of PTB occurring at < 37 weeks under accelerated approval.[16] Furthermore, the Applicant initiated the confirmatory trial in 2009 and provided documentation supporting that this trial could be conducted and completed.

1.4. Hydroxyprogesterone and Progesterone Usage

1.4.1. Use During Pregnancy

FDA conducted a Sentinel query to assess the use of HPC or progesterone during the second or third trimester among pregnancies with live-birth deliveries and their potential reasons for use to characterize the context of real-world use of HPC, the drug substance in Makena. The query captured all pregnancies ending in live birth in the Sentinel Distributed Database, including

[20] Cross-Discipline Team Leader Review dated January 23, 2009 and Complete Response letter dated January 23, 2009.

[21] Engle WA, et al. Committee on Fetus and Newborn, American Academy of Pediatrics. Pediatrics 2007;120(6):1390-401.

[22] McIntire DD, et al. Neonatal mortality and morbidity rates in late preterm births compared with births at term. Obstet Gynecol 2008;111(1):35-41.

[23] Martin JA, et al. Born a bit too early: recent trends in late preterm birth. NCHS Data Brief 2009;Nov(4):1-8.

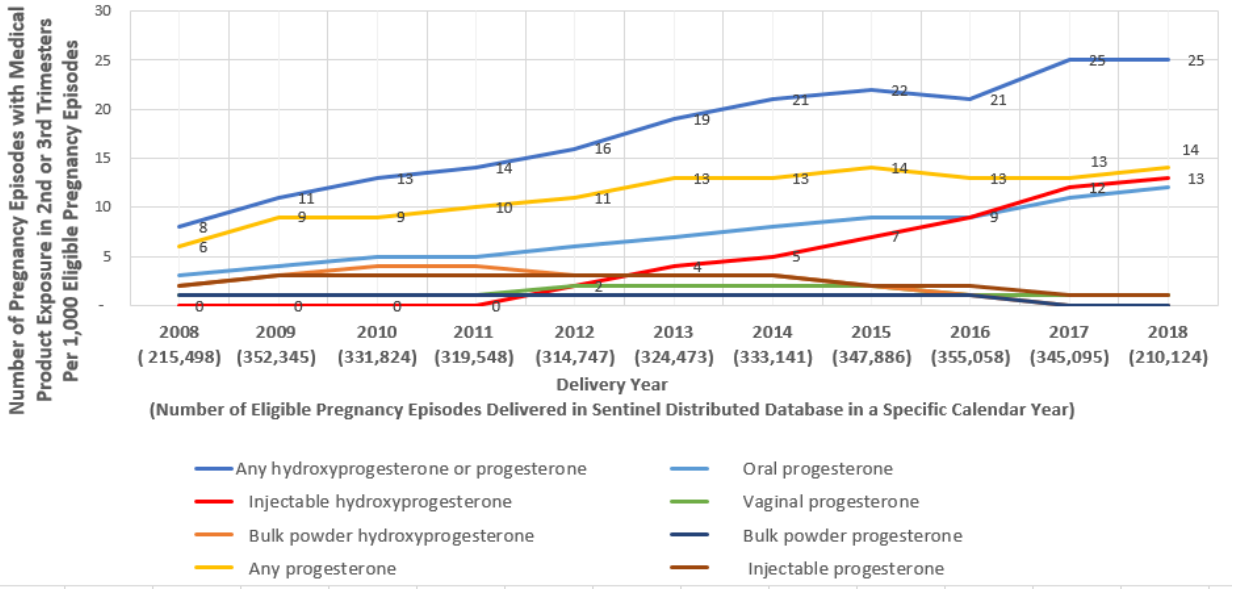
[24] Consortium on Safe Labor, Hibbard JU et al. Respiratory morbidity in late preterm birth. JAMA 2010;304(4):419-25.

singleton and multiple gestations. Progesterone use was included in this analysis because clinical guidelines recommend progesterone treatment for women at risk for preterm delivery.

Methods: This query was conducted in FDA's Sentinel Distributed Database (SDD) using electronic health care data from a distributed network of 15 data partners. The data were primarily comprised of patients with employer-based health care benefits and a small proportion of Medicaid recipients. The study population included women with a live-birth pregnancy (from the current pregnancy) between January 2008 and April 2019 (study period). The exposures of interest were HPC (injectable or bulk powder forms) and progesterone (injectable, oral, vaginal and bulk powder forms). Medical conditions related to potential reasons for HPC or progesterone use were identified by narrow and broad definitions using ICD-9 and ICD-10 diagnosis codes. Included under the narrow definition were diagnosis codes for: (1) history of preterm delivery recorded anytime until one day prior to the start of the current pregnancy, and (2) preterm labor or cervical shortening recorded during the current pregnancy. The broad definition expanded the narrow definition to add the diagnosis for (1) history of preterm labor or cervical shortening recorded anytime until one day prior to the start of the current pregnancy, and (2) preterm delivery recorded during the current pregnancy. Using the diagnostic codes, we could not determine whether the history of preterm delivery was spontaneous or indicated, or whether multiple gestations or other risk factors were present around the time of current pregnancy.

Results: We identified a total of 3,451,121 live-birth pregnancies (from 2,912,911 women) between 2008 and 2019 in FDA's SDD. Note that this number is not a total or annual number of live births in the U.S. Of these, 16,535 pregnancies (5 per 1,000 pregnancies) used injectable HPC during their second or third trimesters and 7,917 used bulk powder HPC (2 per 1,000 pregnancies). In addition, 40,144 (11 per 1,000 pregnancies) pregnancies were exposed to progesterone during the second or third trimesters. In total, approximately 18 per 1,000 pregnancies were exposed to HPC or progesterone during their second or third trimester. The number of exposed pregnancies in each year increased over the study period; the overall the number of exposed pregnancies is modest compared to total pregnancies. The use of HPC or progesterone remains low among pregnancies having a related medical condition, including history of preterm delivery (15%) (Table 3).

Figure 1: Hydroxyprogesterone or Progesterone Use in 2nd or 3rd Trimesters Among 3,449,739, Live-Birth Pregnancy Episodes With Live-Birth Deliveries in the Sentinel Distributed Database Between January 1, 2008, and December 31, 2018, by Delivery Year[1]



[1] Data from 2019 was incomplete and excluded from the figure

Table 3: Proportion of Total Pregnancy Episodes With Related Conditions and With Any Prevalent Hydroxyprogesterone or Progesterone Use During 2nd or 3rd Trimesters Among Women With Live-Birth Deliveries in Sentinel Distributed Database Between January 1, 2008, and April 30, 2019

Related Conditions	Total Number of Pregnancy Episodes with the Related Condition of Interest	Pregnancy Episodes (%) with the Related Conditions of Interest and Any Hydroxyprogesterone or Progesterone Use in the 2nd or 3rd Trimesters
	N	N (%)
Narrow Definition of Related Conditions		
History of preterm delivery[1]	82,255	12,416 (15%)
Preterm labor during the current pregnancy[2]	509,832	29,252 (6%)
Cervical shortening during the current pregnancy[2]	64,557	16,448 (26%)
Any of the narrowly defined conditions above	591,908	40,185 (7%)
Broad Definition of Related Conditions		
History of preterm labor or delivery[1] OR recorded personal history of preterm labor[2]	307,269	34,337 (11%)
Preterm labor or delivery during the current pregnancy[2]	657,719	34,809 (5%)
History of cervical shortening or cervical shortening during the current pregnancy[3]	73,899	17,857 (24%)
Any of the broadly defined conditions above[3]	860,043	51,152 (6%)

[1]Evaluated throughout available enrollment history until the day before pregnancy start date.
[2]Evaluated the day after pregnancy start date until 301 days after pregnancy start date.
[3]Evaluated throughout available enrollment history until 301 days after pregnancy start date.

Among pregnancies exposed to HPC or progesterone, 65% and 83% had at least one related medical condition by narrow and broad definitions, respectively (Table 4), most commonly preterm labor recorded during the current pregnancy. For the pregnancies exposed to injectable HPC, 73% and 98% had at least one narrowly or broadly defined medical condition, respectively.

Table 4: Proportion of Pregnancy Episodes with Related Conditions and Use of Hydroxyprogesterone or Progesterone During 2nd or 3rd Trimesters Among Women With Live-Birth Deliveries in Sentinel Distributed Database Between January 1, 2008, and April 30, 2019

	Any hydroxyprogesterone or progesterone		Hydroxyprogesterone				Progesterone							
			Injectable		Bulk powder		Any		Injectable		Oral		Vaginal	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Number of Pregnancy Episodes with Medical Product Exposure[1]	61,615		16,535		7,917		40,144		8,561		25,471		5,234	
Narrow Definition of Related Conditions														
History of preterm delivery[2]	12,416	20%	6,443	39%	2,568	32%	4,449	11%	1,646	19%	2,365	9%	318	6%
Preterm labor during the current pregnancy[3]	29,252	47%	8,137	49%	5,050	64%	17,969	45%	4,734	55%	10,337	41%	2,515	48%
Cervical shortening during the current pregnancy[3]	16,448	27%	3,228	20%	1,603	20%	12,650	32%	1,694	20%	8,404	33%	2,349	45%
Any of the narrowly defined conditions above[3]	40,185	65%	12,060	73%	6,240	79%	24,351	61%	5,717	67%	14,638	57%	3,499	67%
Broad Definition of Related Conditions														
History of preterm labor or delivery[2] OR recorded personal history of preterm labor during the current pregnancy[3]	34,337	56%	15,696	95%	6,387	81%	14,875	37%	5,381	63%	7,902	31%	1,285	25%
Preterm labor or delivery during the current pregnancy[3]	34,809	56%	8,861	54%	5,811	73%	22,256	55%	5,710	67%	12,875	51%	3,226	62%
History of cervical shortening or cervical shortening during the current pregnancy[4]	17,857	29%	3,982	24%	1,816	23%	13,199	33%	1,840	21%	8,745	34%	2,396	46%
Any of the broadly defined conditions above[4]	51,152	83%	16,240	98%	7,576	96%	30,268	75%	7,344	86%	18,109	71%	4,155	79%

[1] Numbers on the top row are not exclusive because a pregancy could use more than one medicaton of interest
[2] Evaluated throughout available enrollment history until the day before pregnancy start date.
[3] Evaluated the day after pregnancy start date until 301 days after pregnancy start date.
[4] Evaluated throughout available enrollment history until 301 days after pregnancy start date.

We note several study limitations. First, this analysis did not examine the timing of the related medical conditions relative to the use of HPC or progesterone. Therefore, we interpret the presence of the related medical conditions as possible reasons for use. It should be noted that this analysis captured all live-birth pregnancies in the Sentinel Distributed Database. However, we could not determine whether the recorded diagnosis for a history of preterm delivery was spontaneous or indicated, nor did we examine whether the current pregnancy was singleton or multiple gestation. Therefore, HPC exposed pregnancies may not entirely reflect the approved obstetrical indication of HPC. Second, given that women in the SDD were covered primarily by commercial insurance health plans, our findings may have limited generalizability to women without commercial health insurance. Third, we only examined HPC or progesterone use among pregnancies ending with live births. Lastly, the exposure could be under-estimated owing to the capture of pharmacy dispensing data and medication claims only (no capture of out of pocket payments). Some pharmacies create their own National Drug Codes (NDCs) for compounded HPC which would not have been captured in the analysis.

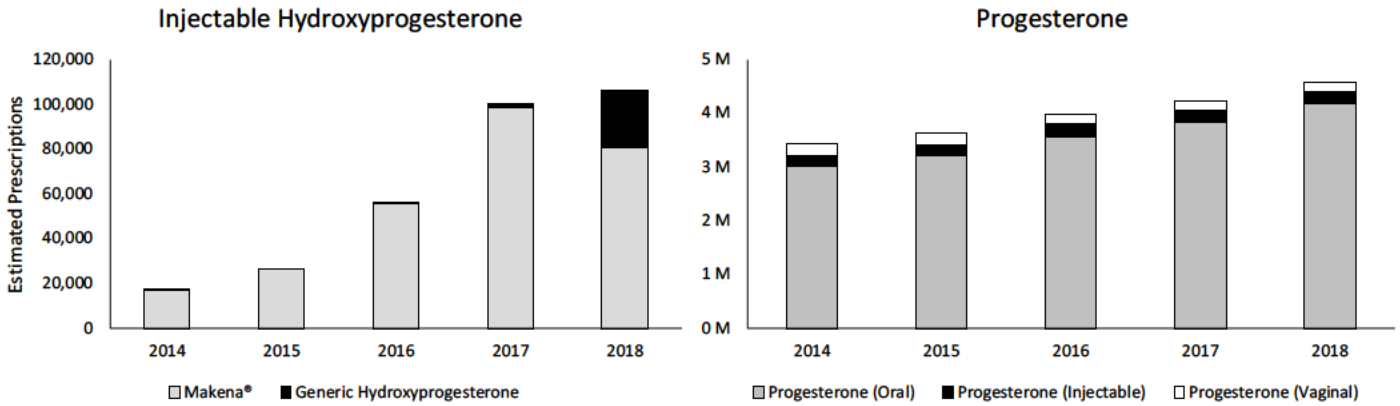
In summary, this analysis found modest use of HPC and progesterone during the second or third trimesters, even among pregnancies with a diagnostic code of a history of preterm delivery (15%). A high percentage (65% and 83% by narrow and broad definitions, respectively) of

pregnancies exposed to HPC or progesterone during their second or third trimester had at least one related medical condition recorded before or during the current pregnancy.

1.4.2. Estimated Use in U.S. Outpatient Settings

FDA analyzed use patterns of injectable HPC and oral, vaginal, or injectable dosage forms of progesterone. Prescriptions for bulk powder forms were excluded due to the inability to determine the final product form and the likelihood that these are underrepresented in the data. We used the Symphony Health PHAST™ Prescription monthly database to estimate the number of prescriptions for injectable HPC and oral, vaginal, or injectable progesterone products dispensed to patients of any age from U.S. outpatient retail or mail order/specialty pharmacies, stratified by molecule and form, annually from 2014 through 2018 (Figure 2). Total prescriptions dispensed for HPC or progesterone products (products with a non-proprietary name of 'hydroxyprogesterone' or 'progesterone') increased 35% from an estimated 3.5 million prescriptions in 2014 to 4.7 million prescriptions in 2018. During this time there was an increase in HPC dispensed prescriptions from an estimated 16,600 prescriptions in 2014 to 106,000 prescriptions in 2018. In 2018, 4.6 million prescriptions (98%) dispensed were for progesterone products.

Figure 2: Estimated Annual Number of Prescriptions Dispensed for Hydroxyprogesterone or Progesterone Products*, Stratified by Molecule and Form, From U.S. Retail or Mail Order/Specialty Pharmacies, Years 2014 to 2018



Prescriptions for bulk powder forms of hydroxyprogesterone and progesterone were not included.
* Products with a non-proprietary name of 'hydroxyprogesterone' or 'progesterone'
Source: Symphony Health PHAST™ Prescription Monthly. Years 2014-2018. Extracted July 2019. File: SH Progesterone and Hydroxyprogesterone Rx 07-29-2019.xlsx

The Symphony Health IDV® Integrated Dataverse was used to obtain the estimated number of 15- to 44-year-old patients who were dispensed prescriptions for injectable HPC and oral, vaginal, or injectable progesterone products from U.S. outpatient retail and mail order/specialty pharmacies, stratified by molecule and form, annually from 2014 through 2018. The total number of patients who were dispensed HPC or progesterone increased by 17% from an estimated 479,000 patients in 2014 to 560,000 patients in 2018 (Table 17 in the Appendix). In 2018, an estimated 42,000 patients (8%) were dispensed prescriptions for HPC, and an estimated 521,000 patients (93%) were dispensed prescriptions for progesterone products. The number of

patients who received a prescription for HPC increased from approximately 8,000 patients in 2014 to 25,500 patients in 2016 and 42,000 patients in 2018.

Table 18 in the Appendix provides the estimated number of drug use mentions of progesterone or HPC products among 15- to 44-year-old women, stratified by molecule and form, associated with a diagnosis as reported on U.S. office-based physician surveys from 2013 through 2018, aggregated. An estimated 50% of HPC use mentions were associated with a diagnosis of supervision of high-risk pregnancy (ICD-10 code O09), of which 78% were associated specifically with supervision of a pregnancy with a history of preterm labor (O09.21, data not shown) and 10% were associated specifically with supervision of elderly primigravida and multigravida (O09.5, data not shown). Twenty percent of HPC use mentions were associated with personal history of preterm labor (Z87.51, data not shown), 13% were associated with encounter for supervision of a normal pregnancy (Z34), and 10% were associated with preterm labor (in the current pregnancy, O60). Among progesterone products, an estimated 42% of progesterone injectable use mentions were associated with supervision of high-risk pregnancy and 41% were associated with female infertility (N97). An estimated 59% of progesterone vaginal use mentions were associated with female infertility.

Table 19 in the Appendix provides the estimated number of drug use mentions among women 15 to 44 years old associated with selected diagnoses as reported on U.S. office-based physician surveys from 2013 through 2018, aggregated. An estimated 42% of office visits with any drug use mentions that were associated with a diagnosis of history of preterm labor (O09.21 or Z87.51) mentioned Makena, and an additional 32% mentioned generic HPC products. Of office visits with drug use mentions that were associated with preterm labor in the current pregnancy, physicians mentioned Makena in 14% of visits. Of office visits associated with cervical shortening, physicians mentioned the use of progesterone products but no other products.

In summary, HPC use increased from 2014 to 2018 with the number of patients treated increasing over the same time period. However, HPC use represents a small proportion of the total use of progesterone in FDA's assessment. The primary use of HPC appeared related to obstetrical diagnoses whereas progesterone was used for both obstetrical and infertility related conditions.

2. Confirmatory Trial—Trial 003

2.1. Development of Trial 003

Please refer to Section 1.3 for a detailed discussion regarding the regulatory history of Makena. After the first non-approval of the NDA in 2006, FDA and the Applicant engaged in discussion regarding a clinical protocol to provide evidence verifying clinical benefit. In 2009, Trial 003 was initiated; the study design mirrored that of Trial 002, except that Trial 003 had coprimary endpoints of delivery prior to 35 weeks and the neonatal morbidity/mortality composite index. When Makena was approved under accelerated approval in 2011, the completion of Trial 003 became a requirement post-approval to verify and describe the clinical benefit of Makena.

Trial 003 was initiated in the United States to ensure at least 10% of subjects would be from the United States and Canada before expanding to Europe. However, after Makena's approval in

2011, enrolling U.S. subjects became increasingly difficult. Additional study sites were subsequently opened in Ukraine and Russia.

2.2. Trial Design

Trial 003 was a multicenter, randomized, double-blind, placebo-controlled clinical trial in women, aged 18 years or older, with a singleton pregnancy, and with a history of a previous singleton spontaneous preterm delivery.

2.2.1. Study Objectives

Primary objectives:

- Determine if treatment with Makena reduces the rate of preterm birth prior to 35^0 weeks of gestation.
- Determine if Makena reduces the rate of neonatal mortality or morbidity.

Secondary objectives:

- Exclude a doubling of the risk of fetal/early infant death, defined as spontaneous abortion/miscarriage (delivery from 16^0 through 19^6 weeks of gestation), early infant death (from minutes after birth until 28 days of life) occurring in livebirths prior to 24 weeks gestation, or stillbirth (antepartum or intrapartum death from 20 weeks gestation through term), in the Makena group compared to the placebo group.
- Determine if Makena reduces the rate of preterm birth prior to 32^0 and 37^0 weeks of gestation, respectively.
- Determine if Makena reduces the rate of stillbirth defined as all stillbirths/fetal deaths/in-utero fetal losses occurring from 20 weeks gestation until term.
- Determine if Makena reduces the rate of neonatal death (from minutes after birth until 28 days life) occurring in livebirths born at 24 weeks gestation or greater.

2.2.2. Trial Design and Conduct

Trial 003 was conducted in the United States, Canada, Russia, Ukraine, Hungary, Spain, Bulgaria, the Czech Republic, and Italy. Eligible subjects were randomized in a 2:1 ratio to receive either Makena or placebo and received weekly injections of study drug from randomization (16^0 through 20^6 weeks of gestation) until 36^6 weeks of gestation or delivery, whichever occurred first.

2.2.3. Eligibility Criteria

Major inclusion criteria:

1. Women aged 18 years or older.
2. Singleton gestation.
3. Estimated gestational age between 16^0 weeks and 20^6 weeks, inclusive, at the time of randomization.
4. Documented history of a previous singleton spontaneous preterm delivery. Spontaneous preterm birth was defined as delivery from 20^0 to 36^6 weeks of gestation following spontaneous preterm labor or preterm premature rupture of membranes (pPROM).

Major exclusion criteria:

1. Multifetal gestation.
2. Known major fetal anomaly or fetal demise;
3. Presence of a uterine anomaly (uterine didelphys or bicornuate uterus)
4. Maternal medical/obstetrical complications or had any significant medical disorder
5. Subjects who received a progestin during the current pregnancy AND met one of the following criteria:
    a. Progestin was administered in the 4 weeks preceding the first dose of study medication.
    b. Subjects received HPC
    c. Progestin was administered by a route other than oral or intra-vaginal.
6. Participation in an antenatal study in which the clinical status or intervention may have influenced gestational age at delivery.
7. Participation in this trial in a previous pregnancy.

2.2.4. Analysis Populations

The Applicant defined the following analysis populations:

- Intent-to-treat (ITT) population: all randomized subjects. Subjects were analyzed by the treatment group to which they were randomized, regardless of the blinded study medication (active or placebo) the subject received.
- Safety population: all subjects who received at least one dose of blinded study medication. Subjects were analyzed by the treatment that they received.
- Liveborn neonatal population: all babies of randomized women in the ITT Population who were liveborn and for whom morbidity/mortality data were available.

2.2.5. Efficacy Endpoints

There were two coprimary endpoints:

- Surrogate endpoint: PTB prior to 35^0 weeks of gestation
    - Scored as a 1 if any of the following events occurred: a delivery occurring from randomization up through 34^6 weeks of gestation, including a miscarriage occurring from 16^0 through 19^6 weeks of gestation, and an elective abortion.
    - Otherwise, scored as a 0.

- Clinical endpoint: Composite neonatal morbidity and mortality index
    - Scored as a 1 if the liveborn neonate had any of the following events occur at any time during the birth hospitalization up through discharge from the neonatal intensive care unit (NICU): neonatal death, grade 3 or 4 intraventricular hemorrhage (IVH), respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), or proven sepsis.
    - Otherwise, scored as a 0.

Key secondary endpoints:

- Neonatal death (from minutes after birth until 28 days of life) occurring in livebirths born at 24 weeks or older gestation
- Preterm birth prior to 32^0 weeks of gestation.

- Preterm birth prior to 37^0 weeks of gestation

Preterm birth endpoints were analyzed using the ITT population and neonatal endpoints were analyzed using the liveborn neonatal population.

The study was designed to detect a 30% reduction in PTB $<35^0$ weeks (from 30% to 21%) and 35% reduction (17% to 11%) in the neonatal composite index, based on the findings from Trial 002. An estimated sample size of 1707 provided at least 90% power to detect the hypothesized difference at alpha level 0.05, and approximately 83% power to rule out a doubling of risk of fetal/early infant death (upper bound of the 95% confidence interval of relative risk <2).

2.2.6. Statistical Analysis Methods

2.2.6.1. Primary Analyses

For each of the coprimary efficacy endpoints, the number and percentage of subjects for the event were presented by treatment groups. Statistical significance between Makena and placebo treatments for each endpoint was determined using a Cochran–Mantel–Haenszel test (CMH) stratified by gestational age at randomization (16^0 to 17^6 weeks and 18^0 to 20^6 weeks).

The interaction between treatment and gestational age at the time of randomization was assessed by a logistic regression model of preterm delivery prior to 35^0 weeks of gestation with terms for treatment, gestational age at randomization stratum, and treatment-by-gestational age at randomization stratum interaction. A similar analysis was performed for the neonatal composite index.

2.2.6.2. Exploratory Analyses

After Trial 003 failed to demonstrate efficacy with the coprimary endpoints, the Applicant conducted a series of exploratory subgroup analyses to understand the potential reasons for the negative findings in Trial 003. The Applicant analyzed the coprimary efficacy endpoints by subgroups defined in Table 5 for the overall study population in Trial 003 and its U.S. subgroup.

Table 5: Trial 003 Subgroup Categories

Subgroup	Categories
Geographic region	U.S., Non-U.S.
Gestational age at randomization	16^0-17^6 weeks, 18^0-20^6 weeks
Gestational age at qualifying delivery*	20^0-<28^0 weeks, 28^0-<32^0 weeks, 32^0-<35^0 weeks, 35^0-<37^0 Weeks
Gestational age at earliest prior PTBs	0-<20^0, 20^0-<28^0, 28^0-<32^0, 32^0-<35^0, 35^0-<37^0
Number of previous PTBs	1, 2, ≥3
Cervical length at randomization	<25 mm ≥25 mm
BMI before pregnancy (kg/m^2)	<18.5, 18.5 - <25, 25-<30, ≥30
Any substance use during pregnancy	Yes, No
Smoking	Yes, No
Alcohol	Yes, No
Illicit drugs	Yes, No
Race	Non-Hispanic black, non-Hispanic non-black
Ethnicity	Hispanic, non-Hispanic
Years of education	≤12, >12

* Qualifying delivery is the most recent preterm delivery.

Generally, FDA does not support unplanned exploratory subgroups analyses, especially when the overall result does not demonstrate efficacy. There are multiple reasons to not consider exploratory subgroup analyses to support establishing efficacy when treatment benefit in the overall population is not significant (FDA draft guidance on multiple endpoints in clinical trials,[25] E17 General Principles for Planning and Design of Multi-Regional Clinical Trials,[26] and E9 Statistical Principles for Clinical Trials[27]). The major statistical reason is inflation of type I error, that is, the heightened probability of incorrectly concluding treatment benefit. When such post-hoc subgroup analyses are used to search for evidence of benefit, there is a high probability that any observed favorable subgroup results are due to chance alone. Therefore, FDA considers exploratory analyses hypothesis-generating.

2.3. Trial Results

2.3.1. Subject Disposition

A total of 1708 subjects were randomized to either Makena (n=1130) or placebo (n=578). Almost all (99%) subjects completed the study and completed treatment (93%). Russia, Ukraine and the U.S. were the three highest enrolling countries, randomizing 621 (36%), 420 (25%) and 391 (23%) subjects, respectively, followed by Hungary, Spain, Bulgaria, Canada, the Czech Republic, and Italy, which each had less than 100 subjects (16% of all subjects).

[25] https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm536750.pdf

[26] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM519603.pdf

[27] https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073137.pdf

Table 6: Trial 003 Subject Disposition

	Makena, N(%)	Placebo, N(%)
Subjects randomized (ITT population)	1130	578
Subjects who received at least one dose of study drug (safety population)	1128 (99.8)	578 (100)
Liveborn infant with morbidity data available (liveborn neonatal population)	1091 (96.5)	560 (96.9)
Subjects withdrawing from study	18 (1.6)	6 (1.0)
Subjects discontinuing study drug	80 (7.1)	43 (7.4)

Source: Applicant's study report

2.3.2. Demographics and Baseline Characteristics

The Makena and placebo groups were comparable across all demographic and baseline characteristics. The mean age was 30 years and pre-pregnancy BMI was 24.4 kg/m^2. Of the randomized subjects, 88% were white, 7% were black, and the rest included Native Hawaiian/Pacific Islanders, Asian and American Indian or Alaska native, mixed race and other. Almost all black subjects were from the United States. Approximately 10% of women were never married or divorced/widowed/separated, approximately 8% smoked, approximately 3% consumed alcohol, and 1.3% used illicit drugs.

The treatment groups were also well balanced with respect to obstetrical characteristics in the current and previous pregnancies. Slightly more subjects initiated study drug between 18^0 to 20^6 weeks of gestation (56% Makena, 58% placebo) than between 16^0 to17^6 weeks (44% Makena, 41% placebo). Overall, the median estimated gestational age at randomization was 18.1 weeks for the Makena group and 18.4 weeks for the placebo group.

2.3.3. Primary Efficacy Results

The neonatal composite index was scored as positive (value of 1) in 5.4% and 5.2% of liveborn infants in the Makena and placebo groups, respectively, with a difference of 0.2% (95% CI: -2.0%, 2.5%) as shown in Table 7. The rate of preterm births prior to 35^0 weeks gestation was 11.0% and 11.5% in the Makena and placebo groups, respectively, with a difference of -0.6% (95% CI: -3.8%, 2.6%). The treatment effect of Makena compared to placebo was not statistically significant for both coprimary endpoints.

The rates of preterm birth prior to 32 weeks gestation and prior to 37 weeks gestation were also not different between the Makena and placebo groups.

Table 7: Trial 003 Efficacy Results

Efficacy Endpoints	Makena (N=1130)	Placebo (N=578)	Difference (95% CI)*	P-value*
Neonatal composite index	5.4% (59/1091)	5.2% (29/560)	0.2% (-2.0, 2.5)	0.84
PTB <35^0 weeks (%)	11.0% (122/1113)	11.5% (66/574)	-0.6% (-3.8, 2.6)	0.72
PTB <32^0 weeks (%)	4.8% (54/1116)	5.2% (30/574)	-0.4% (-2.8, 1.7)	
PTB <37^0 weeks (%)	23.1% (257/1112)	21.9% (125/572)	1.3% (-3.0, 5.4)	

Abbreviations: N: number of randomized subjects, CI: confidence interval, PTB: preterm birth
*Difference, 95% CI and P-value were from CMH method stratified by gestational age at randomization
Source: FDA analysis

2.3.4. Exploratory Analyses Results

Applicant's subgroup analysis results: The Applicant's results for the subgroup analyses of the coprimary efficacy endpoints are presented in Table 21 and Table 22 in the Appendix.

FDA's subgroup analysis results:
FDA reviewed all results and conducted subgroup analyses by region and race because these subgroups are evaluated by FDA routinely. Also, they are important subgroups that differentiate the study populations between Trial 003 and Trial 002.

1. **By geographic region (U.S. versus non-U.S.)**

The Applicant asserts that the overall lower than expected rate of study outcomes substantially limited the ability of Trial 003 to assess the effects of Makena on these outcomes. The Applicant also believes that the lower rate of PTB in Trial 003 could be accounted for by significant geographic differences in PTB rates, where Russia and Ukraine enrolled more subjects but had much lower rates than the United States.

Generally, FDA does not support unplanned subgroup analyses but performed exploratory analysis by region (U.S. versus non-U.S.) to examine whether there were potentially important differences in treatment benefit between U.S. and non-U.S. patients in Trial 003.

For Trial 003, FDA calculated the rate difference between the Makena and placebo groups for each coprimary endpoint, and also the secondary endpoints of birth prior to 32 and 37 weeks gestation, using two methodologies, a stratified CMH method and shrinkage estimation through Bayesian modeling. Traditional subgroup analysis evaluates a particular subgroup category independently from other subgroup categories and relies only on the data from the subjects in that particular category, whereas the Bayesian shrinkage estimation analysis evaluates all subgroup categories jointly. In any trial, some subgroups will perform well, and others will perform poorly. The traditional subgroup analysis is likely to have an increase in the overall error of the estimates compared with the shrinkage analysis, which borrows strength across subgroups.

In the U.S. subgroup of Trial 003, both the neonatal composite index and preterm birth prior to 35 weeks endpoints showed no evidence of a treatment effect using stratified CMH and shrinkage estimation. Although the point estimates of -2.2%, based on the CMH analytic method, for the coprimary endpoints in the U.S. subgroup are in the direction of a beneficial treatment effect, the 95% confidence intervals around these point estimates include 0, indicating

no evidence of effect even in these exploratory subgroup analyses. Similarly, no evidence of a treatment effect was seen for the endpoints of delivery < 37 weeks or < 32 weeks. In addition, the interaction between treatment and region for each coprimary endpoint was assessed by a logistic regression model with treatment, region and treatment-by-region interaction; no significant interaction effect was noted. This Trial 003 subgroup analysis did not show that Makena had a favorable treatment effect compared to placebo for either coprimary endpoints in either the U.S. or non-U.S. region (see Table 8). The lack of evidence of an interaction between region and treatment and the lack of evidence of a treatment effect within the U.S. subgroup in Trial 003 does not provide support for regional differences explaining the differences in results between Trial 002 and 003.

Table 8: Trial 003 Results of Efficacy Endpoints by Region (U.S. vs. non-U.S.)

			Difference (95%CI) Makena vs. Placebo	
	Makena (N=1130)	**Placebo (N = 578)**	**Stratified CMH**	**Shrinkage Estimation**
Neonatal composite index	(N=1091)	(N=560)		
U.S.	7.1% (18/252)	9.5% (12/126)	-2.2% (-8.3, 3.9)	-0.2% (-4.9, 2.8)
Non-U.S.	4.9% (41/839)	3.9% (17/434)	1.0% (-1.4, 3.3)	0.6% (-1.6, 2.8)
Preterm birth <35^0 weeks gestation	(N=1113)	(N=574)		
U.S.	15.6% (40/256)	17.6% (23/131)	-2.2% (-10.1, 5.7)	-0.8% (-6.0, 3.5)
Non-U.S.	9.6% (82/857)	9.7% (43/443)	-0.2% (-3.6, 3.2)	0.4% (-3.6, 2.8)
Preterm birth <32^0 weeks gestation	(N=1116)	(N=574)		
U.S.	5.5% (14/256)	9.2% (12/131)	-3.9% (-9.6, 1.7)	-0.6% (-8.4, 3.8)
Non-U.S.	4.7% (40/860)	4.1% (18/443)	0.6% (-1.7, 2.9)	0.5% (-1.8, 2.8)
Preterm birth <37^0 weeks gestation	(N=1112)	(N=572)		
U.S.	33.2% (85/256)	28.2% (37/131)	4.7% (-5.0, 14.3)	1.8% (-3.6, 9.0)
Non-U.S.	20.1% (172/856)	20.0 % (88/441)	0.2% (-4.4, 4.8)	0.9% (-3.5, 5.2)

Source: FDA analysis

2. By race (black/African American vs. non-black/African American)

FDA conducted a subgroup analysis by race (black and non-black) for Trial 003. This race subgroup analysis did not provide evidence that Makena had a treatment effect on either coprimary efficacy endpoints in the black or non-black subgroups.

Table 9: Trial 003 Results of Coprimary Efficacy Endpoints by Race*

	Makena (N=1130)	Placebo (N=578)	Difference (95%CI)
Neonatal composite index			
Black/African American	8.7% (6/69)	7.5% (3/40)	0.8% (-9.9,11.5)
Non-black/African American	5.2% (53/1022)	5.0% (26/520)	0.2% (-2.1, 2.5)
PTB <35^0 weeks gestation			
Black/African American	23.6% (17/72)	19.5% (8/41)	3.0% (-12.5, 18.5)
Non-black/African American	10.1% (105/1041)	10.9% (58/533)	-0.8% (-4.1, 2.4)

*This is based on the entire Trial 003 study population
Source: FDA analysis

Considering the Applicant's and FDA's subgroup analyses results, Makena did not demonstrate any favorable effect (positive finding with nominal statistical significance) over placebo in the key efficacy endpoints in any of the evaluated subgroups.

2.4. Comparisons Between Trial 003 and Trial 002

FDA does not generally support cross-study comparisons to draw efficacy conclusions. Both Trials 003 and 002 were well-controlled and well-conducted, such that each should provide evidence of efficacy on its own merit. Nevertheless, we explored the potential for significant differences in key aspects between Trials 003 and 002 that might clarify their divergent results.

Study design:
Trials 002 and 003 were nearly identical in design. However, trial 002 was conducted entirely in the United States between 1999 to 2002 with preterm birth <37 weeks as the primary efficacy endpoint. Trial 003 was a multinational trial conducted between 2009 to 2018 with coprimary endpoints of a neonatal composite index and preterm birth <35 weeks and was approximately 3.5 times larger than Trial 002. Trial 003 was powered to detect the treatment difference in the coprimary endpoints based on the effect size observed in Trial 002.

Study populations and trial outcomes:
Trial 003 had the following notable differences compared to Trial 002:

Table 10: Comparisons of Selected Characteristics Between Trial 003 and Trial 002

	Trial 003 Overall (N=1708)	Trial 003 U.S. Subgroup (N=391)	Trial 002 (N=463)
Demographics			
Black race	7%	29%	59%
Single or without a partner	10%	31%	50%
Risk factors			
Use of substance* during pregnancy	10%	28%	26%**
Gestational age of qualifying delivery (weeks)	32	33	31
History of more than one previous PTB	15%	27%	28%/41%***
Rate PTB <35 weeks in placebo group+	12%	18%	30%
Rate PTB <37 weeks in placebo group+	22%	28%	55%

*Including tobacco, alcohol, illicit drugs
**Trial 002 collected information on substance use prior to the study pregnancy and not during the pregnancy; 26% is expected to be the higher end of the estimate because it assumes that all women who used substance prior to the pregnancy continued substance use after becoming pregnant.
***HPC – 28%; Placebo – 41%
+It is assumed that the rate in the placebo group approximates that of the contemporaneous intended population

The overall study population of Trial 003 appeared to be at lower risk for factors that might affect the risk of PTB. The 003-U.S. subgroup, however, was more similar to the Trial 002 study population (see Table 10). Yet, unlike Trial 002, there was no consistent evidence of benefit of Makena over placebo in the U.S. subgroup of Trial 003 (see Table 8). As noted above, no statistically significant interaction was seen between treatment and region in Trial 003.

In its briefing document, the Applicant presented post-hoc efficacy analyses exploring a potential relationship between efficacy and the proportion of subjects in a trial with more than one of 5 selective risk factors (history of > 1 prior PTB, black race, substance use in pregnancy, ≤ 12 years of education, unmarried with no partner). The Applicant concluded that Trial 002 had the "highest" risk population (based on the observation that this trial had the highest proportion of study subjects with more than one of these 5 factors), followed by the Trial 003-U.S. subgroup, and then the overall Trial 003 population as being the relatively lowest risk population. The Applicant's analysis showed a trend toward decreasing efficacy in subpopulations the Applicant considered as lower risk. As described earlier, subgroup analyses, especially when conducted post-hoc when the study findings are known, are exploratory and cannot be relied upon for inferences of efficacy.

In addition, it is challenging to identify specific patient subpopulations that may be more responsive to treatment based on the totality of the data. FDA conducted exploratory analyses of Trial 003 using logistic regression models for each coprimary efficacy endpoint with treatment, region, each of the aforementioned 5 risk factors, and its interaction with treatment. These analyses do not provide convincing evidence of efficacy over placebo in any subpopulation and there is no statistically significant interaction between Makena and any of these risk factors. Analogous analyses in the Trial 003-U.S. subgroup produced similar results. In summary, although these risk factors may have an impact on the overall PTB or neonatal composite index rate, there was no evidence in Trial 003 that they impact the treatment effect nor was there consistent convincing evidence of an effect within a specific subpopulation across the two trials. For example, while black women in the U.S. have a higher rate of PTB compared to non-black

women, there was no interaction between race (blacks vs. non-blacks) and treatment effect in Trial 002 or Trial 003, nor was there evidence of an effect in the U.S. subgroup in Trial 003. Similarly, women with > 1 prior PTB are considered at higher risk of having recurrent PTB. However, there was no consistent trend in treatment benefit in this population (see Table 22). In Trial 002, these women had a treatment benefit compared to placebo in reduced rate of delivery < 35 weeks (30% Makena vs. 44% placebo). This benefit was not observed in Trial 003, where women with > 1 PTB randomized to Makena had higher rates of birth < 35 weeks compared to placebo (Trial 003 overall: 26% Makena vs. 19% placebo; Trial 003 US subgroup: 25% Makena vs. 17% placebo). Importantly, Makena is approved in women with a singleton pregnancy and a prior sPTB, and evidence of efficacy must be based on that intended population.

In summary, Trial 003 did not demonstrate a treatment benefit of Makena on reducing the neonatal composite index or the rate of spontaneous preterm birth prior to 35 weeks gestation, nor was there evidence of a treatment benefit on the rate of spontaneous preterm birth prior to 37 weeks or 32 weeks gestation. The significant statistical limitations with exploratory subgroup analyses preclude reliable inference of efficacy based on findings from these analyses.

3. Other Evidence of Effects of Progesterone on Preterm Birth

There are published data on other progesterone formulations that have been investigated for the treatment of PTB. To explore the consistency of results, FDA evaluated pertinent published literature on the effect of progesterone on the risk of PTB from randomized, placebo-controlled trials and recent, larger meta-analyses. In its briefing document, the Applicant references several studies that evaluated 17-HPC.[28,29,30,31,32,33] However, most of these publications are not applicable to Makena's approved use because the studies assessed different clinical outcomes (early recurrent pregnancy losses or the prevention of preterm labor). There are additional publications that evaluated the effect of hydroxyprogesterone caproate intramuscular injections on pregnancy outcomes (with dosing regimens ranging from 500 mg weekly or twice weekly to

[28] Levine L. Habitual abortion. A controlled study of progestational therapy. West J Surg Obstet Gynecol. 1964;72:30-36.

[29] Papiernik-Berkhauser E. Double blind study of an agent to prevent pre-term delivery among women at increased risk. Edition Schering. 1970;Serie IV(fiche 3):65-68.

[30] Johnson JWC, et al. Efficacy of 17α-hydroxyprogesterone caproate in the prevention of premature labor. New Engl J Med. 1975;293:675-680.

[31] Yemini M, et al. Prevention of premature labor by 17 alpha-hydroxyprogesterone caproate. Am J Obstet Gynecol. 1985:151(5):574-577.

[32] Suvonnakote T. Prevention of pre-term labour with progesterone. J Med Assoc Thailand. 1986;69(10):537-542.

[33] Saghafi N, et al. Efficacy of 17α-hydroxyprogesterone caproate in the prevention of preterm delivery. J Obstet Gynaecol Res. 2011;37(10):1342-1345.

1000 mg weekly); however, they are not discussed further here because of the smaller sample size (80 subjects)[34] or the absence of a concurrent control group.[35,36,37,38]

3.1. Randomized, Placebo-Controlled Clinical Trials

The following six placebo-controlled trials evaluated the treatment effect of progesterone on preterm birth and included pregnant women with a history of a prior sPTB. Note that all these trials evaluated vaginal progesterone.

- The 2003 da Fonseca et al. publication reported findings from a single center trial in Brazil that randomized 142 women with a current singleton pregnancy and a history of previous PTB, cerclage, or uterine malformation in a 1:1 ratio to daily vaginal progesterone insert (100 mg) or placebo.[39] Study drug was applied from 24 to 34 weeks of gestation. The majority (>90%) of women enrolled had previous PTB (mean gestational age at delivery 33 weeks). The rate of PTB <37 weeks was 14% in the progesterone group compared to 29% with placebo (p=0.03).
- The 2007 O'Brien et al. publication reported findings from an international trial that randomized 659 women with a singleton pregnancy and a prior singleton sPTB (delivery between 20^0 and 35^0 weeks of gestation) in a 1:1 ratio to daily vaginal progesterone (8% gel, 90 mg) or placebo starting at 18 to 22^6 weeks until 37 weeks or delivery.[40] Both treatment groups had normal cervical length at randomization (3.7 cm). The primary endpoint, the rate of PTB ≤32 weeks, was not statistically different between the two study groups (10% progesterone vs. 11% placebo, odds ratio: 0.9). Similar results were seen for rate of PTB <37 weeks (42% progesterone vs. 41% placebo, odds ratio: 1.08) and ≤35 weeks (23% progesterone vs. 27% placebo., odds ratio: 0.9). No differences were seen in neonatal outcome (Apgar score, birth weight, NICU admission, respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and death).

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[34] Hauth JC, et al. The effect of 17 alpha- hydroxyprogesterone caproate on pregnancy outcome in an active-duty military population. Am J Obstet Gynecol. 1983;146(2):187-190.

[35] Katz Z, et al. Teratogenicity of progestogens given during the first trimester of pregnancy. Obstet Gynecol. 1985;65(6):775-780.

[36] Rozenberg P, Chauveaud A, Deruelle P, et al. Prevention of preterm delivery after successful tocolysis in preterm labor by 17 alpha-hydroxyprogesterone caproate: a randomized controlled trial. Am J Obstet Gynecol. 2012;206(3):206 e1-9.

[37] Senat MV, Porcher R, Winer N, et al. Prevention of preterm delivery by 17 alpha-hydroxyprogesterone caproate in asymptomatic twin pregnancies with a short cervix: a randomized controlled trial. Am J Obstet Gynecol. 2013;208(3):194 e1-8.

[38] Winer N, Bretelle F, Senat MV, et al. 17 alpha-hydroxyprogesterone caproate does not prolong pregnancy or reduce the rate of preterm birth in women at high risk for preterm delivery and a short cervix: a randomized controlled trial. Am J Obstet Gynecol. 2015;212(4):485 e481-485 e410.

[39] Da Fonseca EB, et al. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: A randomized placebo-controlled double-blind study. Am J Obstet Gynecol. 2003 Feb;188(2):419-24

[40] O'Brien JM, et al. Progesterone vaginal gel for the reduction of recurrent preterm birth: primary results from a randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol. 2007;30: 687 – 696

- The 2007 Fonseca et al. publication reported findings from an international trial that randomized, in a 1:1 ratio, 250 women with a singleton (N=226) or twin (N=24) pregnancy and a short cervix to daily 200 mg micronized progesterone capsule or placebo.[41] The qualifying risk factor was a cervical length ≤15 mm identified incidentally on routine anatomy ultrasound performed at 20 to 24 weeks of gestation, irrespective of history of PTB; the majority of women (>50%) were nulliparous, approximately a third had no prior PTBs, and 15% had a history of one or more PTB. The study medication was used from 24 to 33^6 weeks of gestation. The primary endpoint was spontaneous delivery <34 weeks. The rate of PTB <34 weeks was 19% in the progesterone group compared to 34% in the placebo group, and this difference was statistically significant (relative risk: 0.56; p=0.007). There was no between-group difference for birthweight, fetal/neonatal death, admission to the NICU or major adverse neonatal outcomes before discharge. Among women with a history of PTB (N=38), progesterone administration did not reduce the incidence of PTB before 34 weeks (95% confidence for relative risk included 1).
- In 2011, Hassan et al. reported results of an international (23 U.S. and 21 non-U.S. sites) trial that randomized 465 asymptomatic women with a singleton pregnancy and a shortened cervix (cervical length between 10 to 20 mm) to daily vaginal progesterone (8% gel, 90 mg) or placebo in a 1:1 ratio.[42] Enrollment was stratified by presence/absence of a history of PTB. Women received study drug from 20 to 23^6 weeks until 36^6 weeks or delivery. The primary endpoint was delivery <33 weeks of gestation. The progesterone group had a significantly lower rate of delivery <33 weeks of gestation compared with the placebo (9% vs. 16%, respectively, p=0.02). In women with a history of PTB (13% of the study population) <35 weeks gestation, vaginal progesterone gel administration was not associated with a reduction in the rate of delivery <33 weeks compared to placebo (relative risk: 0.77, 95% CI 0.29-2.06).
- Published in 2016, the OPPTINUM trial was conducted primarily in the United Kingdom and randomized 1228 women with a singleton pregnancy and at risk for PTB in a 1:1 ratio to daily vaginal progesterone (200 mg) or placebo from 22-24 weeks to 34 weeks of gestation.[43] Eligible women had the following risk factors: previous sPTB at ≤34 weeks gestation, a cervical length ≤25 mm, or a positive fetal fibronectin test combined with other clinical risk factors for preterm birth. Three primary outcomes were defined: fetal death or birth <34 weeks (obstetric), a composite of death, brain injury, or bronchopulmonary dysplasia (neonatal), and a standardized cognitive score at 2 years of age (childhood). After adjusting for multiplicity (i.e. overall type I error for multiple outcomes) progesterone was not found to have a significant benefit on the three primary outcomes. In the subgroup of women with a history of sPTB (N=903), there were no

[41] Fonseca EB, et al. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med 2007;357:462-9.

[42] Hassan SS, et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol 2011; 38: 18–31.

[43] Norman JE, et al. Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial. Lancet 2016; 387: 2106–16.

significant differences in the rate of sPTB prior to 34 weeks gestation between the progesterone and placebo groups (odds ratio: 0.82, 95% confidence interval 0.58 to 1.16).

- The 2017 Crowther et al. publication reported findings of the PROGRESS trial, an international trial that randomized 787 women with a singleton or twin pregnancy and a history of sPTB <37 weeks gestation in a 1:1 ratio to vaginal progesterone pessary (100 mg) or placebo.[44] Women were asked to self-administer a vaginal pessary (equivalent to 100 mg vaginal progesterone as active substance) daily from 20 weeks gestation until 34 weeks or delivery. Progesterone treatment had no benefit on the primary outcome of neonatal respiratory distress syndrome (RDS) or other neonatal and maternal morbidities related to preterm birth. Progesterone treatment also had no effect on the incidence of PTB at <37 weeks gestation, a secondary outcome (37% in both treatment groups).

These randomized, placebo-controlled clinical trials enrolled women with varying risk factors for PTB, evaluated different vaginal progesterone doses and formulations, and assessed different outcome measures. Overall, the evidence from these publications does not suggest that vaginal progesterone is beneficial in reducing the risk of preterm birth in women with a history of PTB. Note that FDA has not approved vaginal progesterone for indications related to preterm birth.

3.2. Meta-Analyses

Two published meta-analyses of clinical trials studied the efficacy of progesterone on reducing the risk of PTB: Romero et al. (2018)[45] and Dodd et al. (2013)[46] (Table 11). This section summarizes the meta-analyses, discusses the limitations of each meta-analysis and the regulatory utility of these meta-analyses in supporting the efficacy of Makena. To be consistent with the coprimary endpoint used in Trial 003, we focus on PTB <35 weeks and neonatal composite index.[47]

[44] Crowther et al. Vaginal progesterone pessaries for pregnant women with a previous preterm birth to prevent neonatal respiratory distress syndrome (the PROGRESS study): A multicentre, randomised, placebo-controlled trial. PLoS Med 2017 Sep 26;14(9):e1002390.

[45] Romero R, et al. Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix: a meta-analysis of individual patient data. Am J Obstet Gynecol 2018;218(2): 161-180.

[46] Dodd, Jodie M., et al. Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. *Cochrane Database of Systematic Reviews*7 (2013).

[47] The components of neonatal composite index include neonatal death prior to discharge, grade 3/4 intraventricular hemorrhage, respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, and proven sepsis.

Table 11: Comparison of Study Designs

	Trial 003	Romero et al.	Dodd et al.
Number of subjects (Number of studies)	HPC (Makena): 1,130 Vehicle: 578 (1 RCT)	Progesterone: 498 Placebo: 476 (5 RCTs)	Progesterone: 1,029 Placebo: 869 (11 RCTs)
Study population	Women with singleton birth and history of spontaneous PTB	Women with singleton birth and short cervix	Women with singleton birth and history of spontaneous PTB
Dose	250 mg weekly	90-100 or 200 mg daily	<500 mg weekly or ≥500 mg weekly
Administration	Intramuscular	Intravaginal	Intramuscular, intravaginal, oral, intravenous
Number of subjects from the United States	HPC (Makena): 258 Placebo: 133	Progesterone: 115 Placebo: 117	No U.S. subjects

Source: Reviewer's table

Romero et al. (2018) assessed whether vaginal progesterone prevents PTB and improves perinatal outcomes in women with a singleton gestation and a mid-second trimester, sonographic short cervix (cervical length ≤25 mm). The authors defined a composite neonatal morbidity and mortality[48] outcome. The doses were either 90-100 mg/day or 200 mg/day by intravaginal administration. The authors performed a meta-analysis and estimated the pooled relative risk (RR) with an associated 95% confidence interval (CI). An additional post-hoc subgroup analysis was conducted using an interaction test to examine whether intervention effects differ between the country of enrollment (United States versus other countries). When the heterogeneity of treatment effect was substantial (I^2 >30%), the results were pooled using a random-effect model. Otherwise, a fixed-effect model was used.

The authors' meta-analysis included 5 studies (498 progesterone subjects versus 476 placebo subjects). The meta-analysis showed that vaginal progesterone significantly reduced the risk of PTB <35 weeks (RR [95% CI] = 0.72 [0.58–0.89]) and the risk of composite neonatal morbidity and mortality (RR [95% CI] = 0.59 [0.38–0.91]). A subgroup analysis compared the risk of PTB <33 weeks (PTB <35 weeks and composite neonatal morbidity and mortality not available) between women enrolled from the United States (RR [95% CI] = 0.73 [0.42–1.27]) and women from other countries (RR [95% CI] = 0.59 [0.43–0.80]). The interaction test for subgroup difference did not show significant difference (p = 0.51). Romero et al. included similar proportions of Caucasian subjects (37.2% vs. 39.7%, progesterone and placebo, respectively) and black subjects (36.3% vs. 37.0%, progesterone and placebo, respectively). The subgroup analysis for reduction of PTB among black subjects had a 95% confidence interval that crossed 1 (RR [95% CI] = 0.86 [0.58–1.26]), whereas that of Caucasian subjects had a 95% confidence interval that excluded 1 (RR [95% CI] = 0.45 [0.28–0.73]).

This meta-analysis included subjects with various dose levels (90-100 or 200 mg per day) and the analysis was mainly driven by 3 large studies. In addition, the meta-analysis was underpowered to evaluate interactions. Although both Trial 003 and Romero et al. included

[48] The only difference between neonatal composite index and composite neonatal morbidity and mortality is whether the intraventricular hemorrhages are restricted to grade 3/4 or all grades, respectively.

women with a singleton pregnancy, subjects of Trial 003 had a high prevalence of spontaneous PTB history (100%) with a low prevalence of short cervix (1.6%), while 30% of subjects in the Romero et al. meta-analysis had a history of sPTB history with a high prevalence of short cervix (100%). Romero et al. does not provide information for the approved dose of 250 mg per week administered by intramuscular injection. Because of the difference in study population, formulation, dose levels, and route of administration in Romero et al., the characteristics of the trials in this meta-analysis are not comparable to Trial 003 and the meta-analysis findings do not inform the efficacy of Makena.

Dodd et al. (2013) assessed the benefits and risks of progesterone for the prevention of PTB for women considered to be at increased risk of PTB. This article did not provide a composite neonatal outcome. However, components of the neonatal composite index, except bronchopulmonary dysplasia, were available. The authors performed a meta-analysis and estimated the pooled RR with an associated 95% CI. A random-effect model was employed when the heterogeneity of treatment effect was substantial (I^2 >30%). Otherwise, a fixed-effect model was used.

We focused on the results from the indicated population, women with a singleton pregnancy and history of spontaneous PTB. The authors dichotomized the weekly cumulative dose to either <500 mg or ≥500 mg per week, and the drug was administered through multiple routes: intramuscular, intravaginal, oral, and intravenous. The authors used a total of 11 clinical studies (1,029 progesterone subjects versus 869 placebo subjects) to conduct a meta-analysis in the indicated population. Not all 11 studies were used to analyze the outcomes. Because the result using an outcome of PTB <35 weeks of gestation was not available, we used the authors' outcome of PTB <34 weeks, which concluded that progesterone significantly reduced the risk of PTB (5 studies; RR [95% CI] = 0.31 [0.14–0.69]). The authors reported that neonatal death (6 studies; RR [95% CI] = 0.45 [0.27–0.76]) and necrotizing enterocolitis (3 studies; RR [95% CI] = 0.30 [0.10–0.89]) showed significant risk reduction.

The analysis using 5 studies to estimate the risk of PTB <34 weeks included subjects treated with multiple dose levels and routes of administration. Therefore, the treatment effect of the indicated dose (250 mg) and administration route is unclear. The I^2 from the five studies indicated substantial heterogeneity (I^2 = 56%), raising concerns of whether the trials were too different to be incorporate into the meta-analysis.

Compared to Trial 003, Dodd et al. neither studied the approved dose (250 mg weekly) nor used the intramuscular injection only for administration. Therefore, this meta-analysis is not directly comparable to Trial 003, providing limited inference from the pooled estimate of the treatment effect. None of the five pooled studies that estimated PTB<34 weeks were conducted in the United States; study sites were Iran, Turkey, Brazil, and India.

The two meta-analyses combined different patient populations, formulations, doses and routes of administration. Thus, these studies did not investigate Makena's indicated population, dose, and route of administration and are not comparable to Trial 003. In addition, we do not have access to the patient-level data, individual study protocols and study reports. Because of issues with the

relevancy and the unknown quality of these meta-analyses, the utility of these meta-analyses is limited in addressing the efficacy of Makena.

4. Safety

In Trial 002, total fetal/neonatal deaths included miscarriages (delivery from 16^0 up through 19^6 weeks, stillbirths ([antepartum or intrapartum death] from 20 weeks gestation through term) and neonatal deaths (death of a liveborn born from 20 weeks gestation through term). Of concern was the numerically higher rate of miscarriages and stillbirths in Trial 002. The number of these events were small, and no clear conclusions about the effect of HPC on this safety concern could be made. Trial 003 was powered to exclude a doubling of the risk of fetal/early infant deaths, the primary safety outcome. Fetal/early infant deaths were comprised of the following:

- Spontaneous abortion/miscarriage (delivery from 16^0 up through 19^6 weeks), and
- Stillbirth (antepartum or intrapartum death) from 20 weeks gestation through term, and
- Early fetal death (from minutes after birth until 28 days of life) occurring in livebirths born at < 24 weeks gestation

Fetal and early infant death data from Trial 002 and Trial 003 are juxtaposed in Table 12 and pooled results from both trials are shown in Table 13. Note that the "early fetal death," as defined in 003, was not analyzed as such in Trial 002. The results for "early fetal death" for Trial 002 in Table 12 and Table 13 were analyzed post-hoc for this efficacy supplement. As shown in Table 12, Trial 003 excluded a doubling of the risk of fetal/early infant deaths for Makena (upper bound of 95% was 1.81). When the data from Trial 002 and 003 were pooled, there was no difference in the overall incidence of fetal/early infant deaths with Makena compared to placebo in either trial. There appeared to be a trend toward an increase in stillbirths in both trials; however, the numbers are small, precluding reliable determination of risk. The pooled data from Trials 002 and 003 showed similar results.

Table 12: Fetal and Early Infant Deaths in Trial 002 and Trial 003 (Safety Population)

	Trial 002			Trial 003		
Safety Outcomes N[a], n[b] (%)	**Makena N=310**	**Placebo N=153**	**RR[c] (95% CI)**	**Makena N=1130**	**Placebo N=578**	**RR 95% CI**
Total fetal/early infant deaths[e]	15 (4.8%)	6 (3.9%)	1.22 (0.48, 3.1)	19 (1.7%)	11 (1.9%)	0.87 (0.42, 1.81)
Miscarriages (<20 weeks)	5 (2.4%)	0	N/A	4 (0.5%)	6 (1.3%)	0.32 (0.09, 1.14)
Stillbirths (≥20 weeks)	6 (2.0%)	2 (1.3%)	1.52 (0.31, 7.52)	12 (1.1%)	3 (0.5%)	2.07 (0.59, 7.29)
Early infant deaths	4 (1.3%)	4 (2.6%)	0.49 (0.13, 1.92)	3 (0.3%)	2 (0.4%)	0.73 (0.12, 4.48)

Abbreviations: RR = relative risk, calculated for 17-HPC relative to placebo; CI = confidence interval

[a]N = number of subjects in the Intent to Treat Population in the specified treatment group. The safety population consists of all subjects who received any amount of study medication.

[b]n = number of subjects within a specific category. Percentages are calculated as 100x (n/N)

[c]Relative risk of fetal/early infant death for Makena relative to placebo and is for the Cochran-Mantel-Haenszel test adjusted for gestational age at randomization

[e] Defined as spontaneous abortion/miscarriage, stillbirth, and early fetal death (from minutes after birth until 28 days of life) occurring in livebirths born at <24 weeks gestation

Source: Applicant's analysis (submitted September 25, 2019)

Table 13: Fetal and Early Infant Deaths in Trial 002 and Trial 003 Subjects Combined (Safety Population)

Safety outcomes N[a], n[b] (%)	Trials 002 and 003 Combined		
	Makena N = 1438	Placebo N = 731	RR (95% CI)
Total fetal/neonatal deaths[e]	34 (2.4%)	17 (2.3%)	1.01 (0.57, 1.79)
Miscarriages (<20 weeks)	n = 1075 9 (0.8%)	n = 555 6 (1.1%)	0.73 (0.26, 2.04)
Stillbirths (≥20 weeks)	n = 1429 18 (1.3%)	n = 724 5 (0.7%)	1.86 (0.69, 4.99)
Early infant deaths	n = 1411 7 (0.5%)	n = 720 6 (0.8%)	0.58 (0.20, 1.73)

Source: Applicant's analysis (submitted September 25, 2019)

Birth at 24 weeks is traditionally considered to be the threshold for viability for a preterm neonate, and the Applicant counted only deaths in livebirths born < 24 weeks (early infant death) in the primary safety outcome. FDA, however, considers deaths occurring from minutes after birth until 28 days of life in livebirths born ≥ 20 weeks gestation (neonatal deaths) to be an important safety measurement. These results on fetal and neonatal deaths from Trial 002 and Trial 003 are juxtaposed in Table 14 and pooled results from both trials are shown in Table 15. Overall, these findings are consistent with those above.

Table 14: Fetal and Neonatal Deaths in Trial 002 and Trial 003 (Safety Population)

	Trial 002			Trial 003		
Safety Outcomes N[a], n[b] (%)	Makena N=310	Placebo N=153	RR[c] (95% CI)	Makena N=1130	Placebo N=578	RR 95% CI
Total fetal/neonatal deaths[c]	19 (6.1%)	11 (7.2%)	0.83 (0.41, 1.70)	22 (2.0%)	13 (2.2%)	0.85 (0.43, 1.67)
Miscarriages (<20 weeks)	5 (2.4%)	0	N/A	4 (0.5%)	6 (1.3%)	0.32 (0.09, 1.14)
Stillbirths (≥20 weeks)	6 (2.0%)	2 (1.3%)	1.52 (0.31, 7.52)	12 (1.1%)	3 (0.5%)	2.07 (0.59, 7.29)
Neonatal deaths	8 (2.7%)	9 (6.0%)	0.44 (0.18, 1.12)	6 (0.5%)	4 (0.7%)	0.73 (0.21, 2.58)

[a]N = number of subjects in the Intent to Treat Population in the specified treatment group. The safety population consists of all subjects who received any amount of study medication.

[b]n = number of subjects within a specific category. Percentages are calculated as 100x (n/N)

[c] Defined as spontaneous abortion/miscarriage, stillbirth, and neonatal death (from minutes after birth until 28 days of life) occurring in livebirths born ≥ 20 weeks gestation

Source: Applicant's analysis (submitted September 27, 2019)

Table 15: Fetal and Neonatal Deaths in Trial 002 and Trial 003 Subjects Combined (Safety Population)

Safety outcomes N[a], n[b] (%)	Trials 002 and 003 Combined		
	Makena N = 1438	Placebo N = 731	RR (95% CI)
Total fetal/neonatal deaths[c]	41 (2.9%)	24 (3.3%)	0.85 (0.52, 1.40)
Miscarriages (<20 weeks)	n = 1075 9 (0.8%)	n = 555 6 (1.1%)	0.73 (0.26, 2.04)
Stillbirths (≥20 weeks)	n = 1429 18 (1.3%)	n = 724 5 (0.7%)	1.86 (0.69, 4.99)
Neonatal deaths	n = 1411 14 (1.0%)	n = 720 13 (1.8%)	0.54 (0.25, 1.31)

[a]N = number of subjects in the Intent to Treat Population in the specified treatment group. The safety population consists of all subjects who received any amount of study medication.

[b]n = number of subjects within a specific category. Percentages are calculated as 100x (n/N)

[c] Defined as spontaneous abortion/miscarriage, stillbirth, and neonatal death (from minutes after birth until 28 days of life) occurring in livebirths born ≥ 20 weeks gestation

Source: Applicant's analysis (submitted September 27, 2019)

In Trial 003, the same proportion of subjects in each treatment group (3%) experienced serious treatment-emergent adverse event (TEAE) or maternal pregnancy complications (MPC). The most frequently reported serious TEAE or MPC for subjects treated with Makena were premature separation of placenta (5 subjects, 0.4%), placental insufficiency (4 subjects, 0.4%), and pneumonia (3 subjects, 0.3%). The most frequently reported serious TEAE or MPC for subjects treated with placebo were cholestasis (3 subjects, 0.5%) and premature separation of placenta (2 subjects, 0.3%).

Table 16: Most Common (≥ 2 subjects Overall) Serious TEAE and MPC by Preferred Term in Trial 003 (Safety Population)

Preferred Term	Makena N = 1128 N (%)	Placebo N = 578 N (%)
Subjects with at least one serious TEAE/MPC	**34 (3%)**	**18 (3%)**
Cholestasis	0 (0)	3 (0.5)
Endometritis	1 (0.1)	1 (0.2)
Escherichia sepsis	2 (0.2)	0 (0)
Migraine	1 (0.1)	1 (0.2)
Placental insufficiency	4 (0.4)	1 (0.2)
Pneumonia	3 (0.3)	0 (0)
Premature separation of placenta	5 (0.4)	2 (0.3)
Pyelonephritis	2 (0.2)	1 (0.2)
Wound infection	2 (0.2)	0 (0)

Although the number of fetal and neonatal deaths are too low to draw definitive conclusions, the findings of this safety outcome appear to be similar between placebo and Makena. Otherwise, the safety profile of Makena remains unchanged.

5. Appendix

Table 17: Estimated Annual Number of 15- to 44-Year-Old Patients With Dispensed Prescriptions for Hydroxyprogesterone or Progesterone Products, Stratified by Molecule and Form, From U.S. Retail or Mail Order/Specialty Pharmacies 2014-2018

	2014		2015		2016		2017		2018	
	Patients (N)	%	Patients (N)	%	Patients (N)	%	Patients (N)	%	Patients (N)	%
Total Patients (Hydroxyprogesterone and Progesterone)*	478,567	100%	492,992	100%	513,900	100%	546,499	100%	559,985	100%
All Hydroxyprogesterone	8,039	2%	12,581	3%	25,477	5%	38,744	7%	42,320	8%
Makena®	8,035	100%	12,581	100%	25,126	99%	37,581	97%	31,684	75%
Generic Hydroxyprogesterone Caproate	0	0%	0	0%	117	<1%	769	2%	12,325	29%
All Progesterone Products	471,252	98%	481,858	98%	491,869	96%	510,955	93%	520,992	93%
Progesterone (Oral)	341,067	72%	358,172	74%	377,479	77%	403,335	79%	427,085	82%
Progesterone (Injectable)	94,578	20%	96,532	20%	100,647	20%	102,199	20%	113,736	22%
Progesterone (Vaginal)	117,579	25%	107,735	22%	96,986	20%	89,305	17%	77,378	15%

* Prescriptions for bulk powder forms of hydroxyprogesterone and progesterone were not included.
Source: Symphony Health IDV® Integrated Dataverse. Data years 2014-2018. Extracted August 2019. File: SH UPC Progesterone and Hydroxyprogesterone Pt 08-07-2019.xlsx.
Unique patient counts should not be added across time periods or drug categories due to the possibility of double counting those patients who received multiple products within the same calendar year or over multiple periods in the study. Generic hydroxyprogesterone caproate use in 2016 and 2017 were generic Delalutin products.

Table 18: Diagnoses Associated With the Estimated Number of Progesterone or Hydroxyprogesterone Use Mentions Among 15- to 44-Year-Old Women From U.S. Office-Based Physician Surveys, 2013 Through 2018, Aggregated

January 2013 - December 2018

	Uses (000)	95% CI (000)	% Share
Total Progesterone and Hydroxyprogesterone	**3,786**	**3,401-4,172**	**100%**
Hydroxyprogesterone Inj	**1,592**	**1,342-1,842**	**42%**
O09 Supervision of high-risk pregnancy	797	620-973	50%
Z87.51 Personal history of preterm labor	324	211-437	20%
Z34 Encounter for supervision of normal pregnancy	211	120-302	13%
O60 Preterm labor in current pregnancy	158	79-237	10%
O34 Maternal care for abnormality of pelvic organs	28	<0.5-61	2%
All Others	75	21-130	5%
Progesterone (all forms)	**2,194**	**1,901-2,488**	**58%**
Progesterone oral	**677**	**514-840**	**31%**
O20 Hemorrhage in early pregnancy	80	24-136	12%
N97 Female infertility	79	23-134	12%
Z34 Encounter for supervision of normal pregnancy	68	17-120	10%
N91 Absent, scanty and rare menstruation	68	16-119	10%
O26 Maternal care for pregnancy-related conditions	64	14-114	9%
All Others	318	206-430	47%
Progesterone injectable	**416**	**288-543**	**19%**
O09 Supervision of high-risk pregnancy	173	91-256	42%
N97 Female infertility	169	87-250	41%
O20 Hemorrhage in early pregnancy	41	1-81	10%
O60 Preterm labor in current pregnancy	17	<0.5-43	4%
O34 Maternal care for abnormality of pelvic organs	9	<0.5-28	2%
All Others	7	<0.5-23	2%
Progesterone vaginal	**1,054**	**851-1,258**	**48%**
N97 Female infertility	622	466-779	59%
O09 Supervision of high-risk pregnancy	125	55-195	12%
O20 Hemorrhage in early pregnancy	121	52-190	11%
O26 Maternal care for pregnancy-related conditions	105	41-170	10%
N96 Recurrent pregnancy loss	45	3-87	4%
All Others	36	<0.5-73	3%

Source: Syneos Health Research and Insights, TreatmentAnswers™ with Pain Panel. Data years 2013-2018. Extracted July 2019. File: Progesterone and Hydroxyprogesterone products by diagnosis 07-22-2019.xlsx. Diagnosis data are not directly linked to dispensed prescriptions but obtained from surveys of a sample of 3,200 office-based physicians reporting on patient activity one day a month. Drug use mentions below 100,000 may not represent reliable estimates of use and should be interpreted with caution because the sample size may be very small with corresponding large confidence intervals.

Table 19: Estimated Drug Use Mentions Among 15- to 44-Year-Old Women Associated With Selected Diagnoses From U.S. Office-Based Physician Surveys, 2013-2018, Aggregated

January 2013 through December 2018

	Uses (000)	95% CI Uses (000)	Share %
Current/history preterm labor or cervical shortening	**2,364**	**2,059-2,668**	**100%**
History of preterm labor (O09.21X, Z87.51)	1,277	1,054-1,501	54%
Makena	539	394-685	42%
17-Alpha Hydroxyprogesterone	290	184-397	23%
Hydroxyprogesterone	112	46-178	9%
Prenatal OTC	88	29-146	7%
Prenatal Rx	73	19-126	6%
All Others	175	92-258	14%
Preterm labor in current pregnancy (O60.XXX)	936	744-1,127	40%
Nifedipine	172	90-254	18%
Makena	135	62-207	14%
Procardia	132	60-203	14%
Terbutaline Inj	85	27-143	9%
Betamethasone Inj	75	21-129	8%
All Others	338	223-453	36%
Cervical shortening (O26.87X)	151	74-228	6%
Progesterone vaginal	73	20-127	48%
Prometrium	60	11-109	40%
Prochieve	11	<0.5-32	7%
Crinone	7	<0.5-23	5%

Source: Syneos Health Research and Insights, TreatmentAnswers™ with Pain Panel. Data years 2013-2018. Extracted July 2019. File: Progesterone and Hydroxyprogesterone products by diagnosis 07-22-2019.xlsx. Diagnosis data are not directly linked to dispensed prescriptions but obtained from surveys of a sample of 3,200 office-based physicians reporting on patient activity one day a month. Drug use mentions below 100,000 may not represent reliable estimates of use and should be interpreted with caution because the sample size may be very small with corresponding large confidence intervals.

Table 20: Comparison of Demographics and Baseline Characteristics: Studies 002 and 003

	Trial 003		Trial 003 U.S. subset		Trial 002	
Variable	**Makena (N=1130)**	**Placebo (N=578)**	**Makena (N=258)**	**Placebo (N=133)**	**Makena (N=310)**	**Placebo (N=153)**
Gestational age of qualifying delivery, weeks	31.3 ± 4.4	31.6 ± 4.2	32.5 ± 3.9	32.5 ± 3.9	30.6 ± 4.6	31.3 ± 4.2
Number of previous preterm deliveries						
1 previous PTB, N (%)	964 (85)	494 (86)	187 (72)	97 (73)	224 (72)	90 (59)
>1 previous PTB, N (%)	166 (15)	82 (14)	71 (28)	36 (27)	86 (28)	63 (41)
Number with cervical length <25 mm at randomization, N (%)	18 (2)	9 (2)	13 (5)	3 (2)	NA	NA
Age, years	30 ± 5	30 ± 5	28 ± 5	27 ± 5	26 ± 6	27 ± 5
Race, N (%)						
Black or African American/African Heritage	73 (6)	41 (7)	72 (28)	41 (31)	183 (59)	90 (59)
White	1004 (89)	504 (87)	170 (66)	84 (63)	79 (25)	34 (22)
Asian	23 (2)	22 (4)	4 (2)	2 (2)	2 (1)	1 (1)
Other	30 (3)	11 (2)	12 (5)	6 (5)	3 (1)	2 (1)
Ethnicity, N (%)						
Hispanic or Latino	101 (9)	54 (9)	31 (12)	23 (17)	43 (14)**	26 (17)**
Non-Hispanic or Latino	1029 (91)	524 (91)	227 (88)	110 (83)	267 (86)	127 (83)
Marital Status, N (%)						
Married or living with partner	1013 (90)	522 (90)	180 (70)	91 (68)	159 (51)	71 (46)
Never married	86 (8)	40 (7)	61 (24)	33(25)	119 (38)	64 (42)
Divorced, widowed or separated	31 (3)	16 (3)	17 (7)	9 (7)	32 (10)	18 (12)
BMI before pregnancy	24.3 ± 7.1	24.7 ± 8.7	27.4 ± 11.8	29.3 ± 15.3	26.9 ± 7.9	26.0 ± 7.0
Years of education	13 ± 2	13 ± 2	13 ± 2	13 ± 2	12 ± 2	12 ± 2
Any substance use during pregnancy, N (%)	105 (9)	51 (9)	69 (27)	40 (30)	85 (27)	36 (24)
Smoking	92 (8)	40 (7)	58 (22)	31 (23)	70 (23)	30 (20)
Alcohol	23 (2)	18 (3)	20 (8)	16 (12)	27 (9)	10 (7)
Illicit drugs	15 (1)	8 (1)	15 (6)	8 (6)	11 (4)	4 (3)

**Hispanic or Latino included in both race and ethnicity category for Study 002

Table 21: Summary of Neonatal Composite Index by Subgroups

Neonatal Composite Index, Subgroup	Trial 003 Makena (N=1091)	Trial 003 Placebo (N=560)	Trial 003 U.S. subset Makena (n=252)	Trial 003 U.S. subset Placebo (n=126)	Trial 002 Makena (N=295)	Trial 002 Placebo (N=151)
GA at randomization (weeks)						
16^0-17^6	25/481 (5.2)	12/230 (5.2)	4/93 (4.3)	4/36 (11.1)	12/97 (12.4)	11/47 (23.4)
18^0-20^6	34/610 (5.6)	17/330 (5.2)	14/159 (8.8)	8/90 (8.9)	23/198 (11.6)	15/104 (14.4)
Overall	59/1091 (5.4)	29/560 (5.2)	18/252 (7.1)	12 /126 (9.5)	35/295 (11.9)	26/151 (17.2)
GA of qualifying delivery* (weeks)						
20^0 - $<28^0$	17/221 (7.7)	3/97 (3.1)	3/30 (10.0)	2/17 (11.8)	11/74 (14.9)	9/29 (31.0)
28^0 - $<32^0$	14/198 (7.1)	13/102 (12.7)	3/37 (8.1)	4/18 (22.2)	5/65 (7.7)	5/30 (16.7)
32^0 - $<35^0$	15/339 (4.4)	9/182 (4.9)	3/73 (4.1)	5/39 (12.8)	11/79 (13.9)	9/54 (16.7)
35^0 - $<37^0$	13/330 (3.9)	4/176 (2.3)	9/110 (8.2)	1/51 (2.0)	8/77 (10.4)	3/38 (7.9)
GA of earliest prior PTB** (weeks)						
0 - $<20^0$	24/445 (5.4)	11/228 (4.8)	5/75 (6.7)	3/35 (8.6)	6/46 (13.0)	1/16 (6.3)
20^0 - $<28^0$	13/153 (8.5)	2/71 (2.8)	4/27 (14.8)	1/18 (5.6)	10/47 (21.3)	9/23 (39.1)
28^0 - $<32^0$	9/112 (8.0)	7/59 (11.9)	2/29 (6.9)	3/13 (23.1)	4/39 (10.3)	4/20 (20.0)
32^0 - $<35^0$	7/198 (3.5)	6/99 (6.1)	2/59 (3.4)	4/29 (13.8)	8/55 (14.5)	6/34 (17.6)
35^0 - $<37^0$	6/183 (3.3)	3/102 (2.9)	5/62 (8.1)	1/31 (3.2)	5/40 (12.5)	2/26 (7.7)
Previous PTB, N (%)						
1	43/933 (4.6)	22/478 (4.6)	11/184 (6.0)	8/92 (8.7)	18/210 (8.6)	10/89 (11.2)
>1‡	16/158 (10.1)	7/80 (8.8)	7/78 (9.0)	4/34 (11.8)	17/85 (10.0)	16/62 (25.8)
2	14/125 (11.2)	5/66 (7.6)	6/52 (11.5)	4/28 (14.3)	12/55 (21.8)	8/45 (17.8)
≥3	2/33 (6.1)	2/14 (14.3)	1/16 (6.3)	0/6 (0.0)	5/30 (16.7)	8/17 (47.1)
Cervical length at randomization***, N (%)						
<25 mm	2/17 (11.8)	2/9 (22.2)	1/13 (7.7)	1/3 (33.3)	NA	NA
≥25 mm	44/890 (4.9)	23/444 (5.2)	11/110 (10.0)	10/63 (15.9)	NA	NA
BMI before pregnancy (kg/m^2)						
Underweight (<18.5)	4/80 (5.0)	3/37 (8.1)	0/11 (0)	0/2 (0)	4/25 (16.0)	2/10 (20.0)
Normal (18.5 - <25)	34/629 (5.4)	12/328 (3.7)	7/112 (6.3)	2/49 (4.1)	13/116 (11.2)	14/73 (19.2)
Overweight (25 - <30)	10/249 (4.0)	9/125 (7.2)	6/63 (9.5)	6/34 (17.6)	6/56 (10.7)	5/30 (16.7)
Obese (≥30)	11/133 (8.3)	5/69 (7.2)	5/66 (7.6)	4/41 (9.8)	10/86 (11.6)	5/34 (14.7)

Neonatal Composite Index, Subgroup	Trial 003 Makena (N=1091)	Trial 003 Placebo (N=560)	Trial 003 U.S. subset Makena (n=252)	Trial 003 U.S. subset Placebo (n=126)	Trial 002 Makena (N=295)	Trial 002 Placebo (N=151)
Any substance use during pregnancy, N (%)						
Yes	8/101 (7.9)	5/49 (10.2)	5/67 (7.5)	4/38 (10.5)	12/82 (14.6)	6/35 (17.1)
No	51/990 (5.2)	24/511 (4.7)	13/185 (7.0)	8/88 (9.1)	23/213 (10.8)	20/116 (17.2)
Smoking						
Yes	8/89 (9.0)	4/39 (10.3)	5/57 (8.8)	3/29 (10.3)	10/67 (14.9)	6/29 (20.7)
No	51/1002 (5.1)	25/521 (4.8)	13/195 (6.7)	9/97 (9.3)	25/228 (11.0)	20/122 (16.4)
Alcohol						
Yes	0/23 (0)	4/17 (23.5)	0/19 (0)	3/15 (20.0)	3/26 (11.5)	0/10 (0)
No	59/1068 (5.5)	25/543 (4.6)	18/233 (7.7)	9/111 (8.1)	32/269 (11.9)	26/141 (18.4)
Illicit drugs						
Yes	1/14 (7.1)	1/7 (14.3)	1/13 (7.7)	1/7 (14.3)	2/10 (20.0)	0/4 (0)
No	58/1077 (5.4)	28/553 (5.1)	17/239 (7.1)	11/119 (9.2)	33/285 (11.6)	26/147 (17.7)
Race						
Non-Hispanic black	6/69 (8.7)	3/39 (7.7)	5/68 (7.4)	3/39 (7.7)	22/176 (12.5)	20/89 (22.5)
Non-Hispanic non-black	50/923 (5.4)	23/468 (4.9)	13/153 (8.5)	7/64 (10.9)	8/81 (9.9)	6/36 (16.7)
Ethnicity						
Hispanic	3/99 (3.0)	3/53 (5.7)	0/31 (0)	2/23 (8.7)	5/38 (13.2)	0/26 (0)
Non-Hispanic	56/992 (5.6)	26/507 (5.1)	18/221 (8.1)	10/103 (9.7)	30/257 (11.7)	26/125 (20.8)
Years of education						
≤12	28/458 (6.1)	18/249 (7.2)	9/116 (7.8)	9/69 (13.0)	29/213 (13.6)	18/101 (17.8)
>12	31/632 (4.9)	11/311 (3.5)	9/135 (6.7)	3/57 (5.3)	6/82 (7.3)	8/50 (16.0)

* If more than one prior delivery was sPTB, qualifying delivery was the most recent.
** The earliest PTB may be indicated or spontaneous.
***Cervical length measurement was not captured for all subjects in a treatment group.
GA = gestational age
NA = not available
Source: Applicant Analysis; ǂFDA Analysis.

Table 22: Summary of PTB <35^0 Weeks by Subgroups

Stratification Groups, n/N (%)	Trial 003		Trial 003 U.S. Subset		Trial 02	
	Makena (N=1130)	Placebo (N=578)	Makena (N=258)	Placebo (N=133)	Makena (N=310)	Placebo (N=153)
GA at randomization (weeks)						
16^0-17^6	61/493 (12.4)	31/238 (13.0)	16/96 (16.7)	9/40 (22.5)	22/103 (21.4)	21/47 (44.7)
18^0-20^6	61/620 (9.8)	35/336 (10.4)	24/160 (15.0)	14/91 (15.4)	41/203 (20.2)	26/106 (24.5)
Overall	122/1113 (11.0)	66/574 (11.5)	40/256 (15.6)	23/131 (17.6)	63/306 (20.6)	47/153 (30.7)
GA of qualifying delivery* (weeks)						
20^0 - <28^0	29/229 (12.7)	9/101 (8.9)	7/31 (22.6)	3/18 (16.7)	21/82 (25.6)	13/29 (44.8)
28^0 - <32^0	24/201 (11.9)	20/104 (19.2)	9/37 (24.3)	4/18 (22.2)	12/65 (18.5)	6/30 (20.0)
32^0 - <35^0	36/344 (10.5)	24/186 (12.9)	9/75 (12.0)	10/40 (25.0)	12/81 (14.8)	18/55 (32.7)
35^0 - <37^0	32/336 (9.5)	13/180 (7.2)	14/111 (12.6)	6/54 (11.1)	18/78 (23.1)	10/39 (25.6)
GA of earliest prior PTB** (weeks)						
0 - <20^0	53/459 (11.5)	26/234 (11.1)	13/78 (16.7)	5/36 (13.9)	9/46 (19.6)	3/16 (18.8)
20^0 - <28^0	21/156 (13.5)	7/73 (9.6)	7/27 (25.9)	3/19 (15.8)	21/55 (38.2)	11/23 (47.8)
28^0 - <32^0	15/113 (13.3)	12/60 (20.0)	8/30 (26.7)	3/13 (23.1)	7/39 (17.9)	5/20 (25.0)
32^0 - <35^0	18/201 (9.0)	12/100 (12.0)	5/59 (8.5)	6/29 (20.7)	9/56 (16.1)	13/35 (37.1)
35^0 - <37^0	15/184 (8.2)	9/106 (8.5)	7/62 (11.3)	6/34 (17.6)	10/40 (25.0)	5/26 (19.2)
Previous PTD, N (%)						
1	80/949 (8.4)	51/491 (10.4)	22/185 (11.9)	17/96 (17.7)	37/220 (16.8)	19/90 (21.1)
>1‡	42/164 (25.6)	15/81 (18.5)	18/71 (25.3)	6/35 (17.1)	26/86 (30.2)	28/63 (44.4)
2	29/127 (22.8)	10/67 (14.9)	13/52 (25.0)	4/29 (13.8)	18/56 (32.1)	17/46 (37.0)
≥3	13/37 (35.1)	5/14 (35.7)	5/19 (16.3)	2/6 (33.3)	8/30 (26.7)	11/17 (64.7)
Cervical length at randomization***, N (%)						
<25 mm	4/18 (22.2)	4/9 (44.4)	2/13 (15.4)	1/3 (33.3)	NA	NA
≥25 mm	92/907 (10.1)	45/455 (9.9)	21/112 (18.8)	13/66 (19.7)	NA	NA
BMI before pregnancy						
Underweight (<18.5)	13/83 (15.7)	4/38 (10.5)	0/11 (0)	0/3 (0)	5/25 (20.0)	6/10 (60.0)
Normal (18.5 - <25)	59/637 (9.3)	33/335 (9.9)	20/112 (17.9)	10/51 (19.6)	23/131 (17.6)	26/77 (33.8)
Overweight (25 - <30)	29/255 (11.4)	16/127 (12.6)	9/66 (13.6)	6/34 (17.6)	14/60 (23.3)	10/32 (31.3)
Obese (≥30)	21/138 (15.2)	13/74 (17.6)	11/67 (16.4)	7/43 (16.3)	21/90 (23.3)	5/34 (14.7)

Stratification Groups, n/N (%)	Trial 003		Trial 003 U.S. Subset		Trial 02	
	Makena (N=1130)	Placebo (N=578)	Makena (N=258)	Placebo (N=133)	Makena (N=310)	Placebo (N=153)
Any substance use during pregnancy, N (%)						
Yes	19/105 (18.1)	13/51 (25.5)	11/69 (15.9)	10/40 (25.0)	16/85 (18.8)	16/36 (44.4)
No	103/1008 (10.2)	53/523 (10.1)	29/187 (15.5)	13/91 (14.3)	47/221 (21.3)	31/117 (26.5)
Smoking						
Yes	18/92 (19.6)	11/40 (27.5)	10/58 (17.2)	8/30 (26.7)	13/70 (18.6)	15/30 (50.0)
No	104/1021 (10.2)	55/534 (10.3)	30/198 (15.2)	15/101 (14.9)	50/236 (21.2)	32/123 (26.0)
Alcohol						
Yes	1/23 (4.3)	5/18 (27.8)	1/19 (5.3)	4/16 (25.0)	5/27 (18.5)	2/10 (20.0)
No	121/1090 (11.1)	61/556 (11.0)	39/237 (16.5)	19/115 (16.5)	58/279 (20.8)	45/143 (31.5)
Illicit drugs	2/15 (13.3)	3/8 (37.5)	2/14 (14.3)	3/8 (37.5)	2/11 (18.2)	0/4 (0)
Yes						
No	120/1098 (10.9)	63/566 (11.1)	38/242 (15.7)	20/123(16.3)	61/295 (20.7)	47/149 (31.5)
Race						
Non-Hispanic black	17/72 (23.6)	8/40 (20.0)	16/71 (22.5)	8/40 (20.0)	39/183 (21.3)	32/90 (35.6)
Non-Hispanic non-black	92/940 (9.8)	50/480 (10.4)	19/154 (12.3)	10/68 (14.7)	28/127 (22.0)	15/63 (23.8)
Ethnicity						
Hispanic	13/101 (12.9)	8/54 (14.8)	5/31 (16.1)	5/23 (21.7)	10/41 (24.4)	4/26 (15.4)
Non-Hispanic	109/1012 (10.8)	58/520 (11.2)	35/225 (15.6)	18/108 (16.7)	53/265 (20.0)	43/127 (33.9)
Years of education						
≤12	64/474 (13.5)	40/256 (15.6)	24/120 (20.0)	18/74 (24.3)	49/223 (22.0)	32/103 (31.1)
>12	58/639 (9.1)	26/318 (8.2)	16/136 (11.8)	5/57 (8.8)	14/83 (16.9)	15/50 (30.0)

* If more than one prior delivery was sPTB, qualifying delivery was the most recent.
** The earliest PTB may be indicated or spontaneous.
***Cervical length measurement was not captured for all subjects in a treatment group.
GA = gestational age
NA = not available
Source: Applicant Analysis. ‡FDA Analysis.

EXHIBIT C

Makena® (hydroxyprogesterone caproate injection) Approval and Product Label Remain Unchanged (read more (https://www.amagpharma.com/makena-hydroxyprogesterone-caproate-injection-approval-and-product-label-remain-unchanged/))

Media Contact

Thank you for your interest in learning more about AMAG. Contact Us (https://www.amagpharma.com/about-us/media-contact/)

(mailto:)

(mailto:)

()

Newsroom (https://www.amagpharma.com/newsroom/)

AMAG Files Response to Citizen Petition

January 21, 2020 | AMAG News

Today, AMAG Pharmaceuticals, Inc. submitted its response https://www.regulations.gov/document?D=FDA-2019-P-4683-0005 (https://www.regulations.gov/document?D=FDA-2019-P-4683-0006) with the U.S. Food and Drug Administration (FDA) to a petition filed by Public Citizen's Health Research Group (HRG).

AMAG respectfully disagrees with HRG's request to withdraw FDA approval of Makena® (hydroxyprogesterone caproate injection) and the five FDA-approved generics (which could no longer be marketed if Makena's NDA was withdrawn). The response provides six arguments to support the continued, positive benefit-risk profile of Makena.

1. *Preterm Birth is a Significant Public Health Issue*

Preterm birth is the leading cause of neonatal mortality and morbidity in the U.S., and rates of preterm birth are on the rise in the U.S. Makena and its generics – often referred to as 17P or 17-OHPC, are the only FDA-approved treatment options indicated for reducing the risk of

recurrent preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.

2. *FDA's 2011 Approval of Makena was Appropriate Based on the Landmark Meis Study*

Makena was granted accelerated approval in 2011 based on a clinical trial conducted by the Maternal-Fetal Medicine Units Network, sponsored by the National Institute of Child Health and Human Development, which was published by Meis et al. in the *New England Journal of Medicine*. The Meis study, which was conducted entirely in the U.S., demonstrated that 17P reduced the occurrence of recurrent preterm delivery by approximately one-third compared to placebo. The Meis study continues to provide substantial evidence that supports ongoing access to FDA-approved 17P for this high-risk, orphan population with no FDA-approved alternatives.

3. *The Results of PROLONG Do Not Invalidate the Results of the Meis Study*

The recently completed PROLONG (Progestin's Role in Optimizing Neonatal Gestation) study did not meet its two pre-specified co-primary endpoints. While PROLONG failed to confirm 17P's efficacy, it does not invalidate the results and conclusions from the Meis study. PROLONG, although designed to replicate the Meis study, evaluated a markedly different, international patient population with significantly lower background rates of preterm birth risk with more than 75 percent of subjects being enrolled from outside of the U.S. This lower risk patient population was reflective of the reluctance of U.S. physicians to enroll high-risk patients in a placebo-controlled study rather than prescribe 17P. As a consequence, the rate of recurrent preterm birth was considerably lower than expected, which resulted in PROLONG being underpowered. This unexpectedly lower rate of preterm birth, driven by ex-U.S. enrollment, raises uncertainty about the applicability of PROLONG to the higher risk U.S. population.

Importantly, a favorable maternal and fetal safety profile of 17P was reaffirmed in PROLONG.

Following the release of the PROLONG data, both the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine issued statements, which support the use of 17P in appropriate patients.

4. *FDA Can Ensure Continued Access to 17P*

As FDA has previously noted, they judiciously consider multiple factors, including safety, patient need, and the availability of other treatments when considering whether to withdraw a product approved under accelerated approval. As FDA has recognized, there are many reasons for the outcomes of a trial, including the population used. FDA considers the public's best interest before removing a drug from the market and has long-standing flexibility when considering what constitutes substantial evidence. AMAG is committed to continuing a dialogue with the FDA on feasible ways to generate additional efficacy data while retaining current access for patients.

5. *Withdrawal Would Deprive Women and Their Physicians of the Option of Shared Decision-making*

Removing the only FDA-approved treatment from the market would impact the shared decision-making for pregnant women and their providers. It would leave patients with no effective options or result in a return to compounded 17P with the associated potential efficacy and safety risks. In addition to these concerns, compounded medications lack appropriate labeling to inform patients and providers about potential risks and benefits.

6. *The U.S. has Substantial Health Disparities in Preterm Birth, Which Would Likely be Increased Without Access to FDA-Approved 17P*

The demographic differences between the Meis and PROLONG populations underscore the impact that social determinants of health may have had on the results of both studies. The body of evidence most generalizable to U.S. patients is the Meis study due to its exclusively U.S. enrollment. Withdrawing the only FDA-approved intervention could have the unintended consequence of further exacerbating existing health disparities associated with preterm birth in the most vulnerable patient populations.

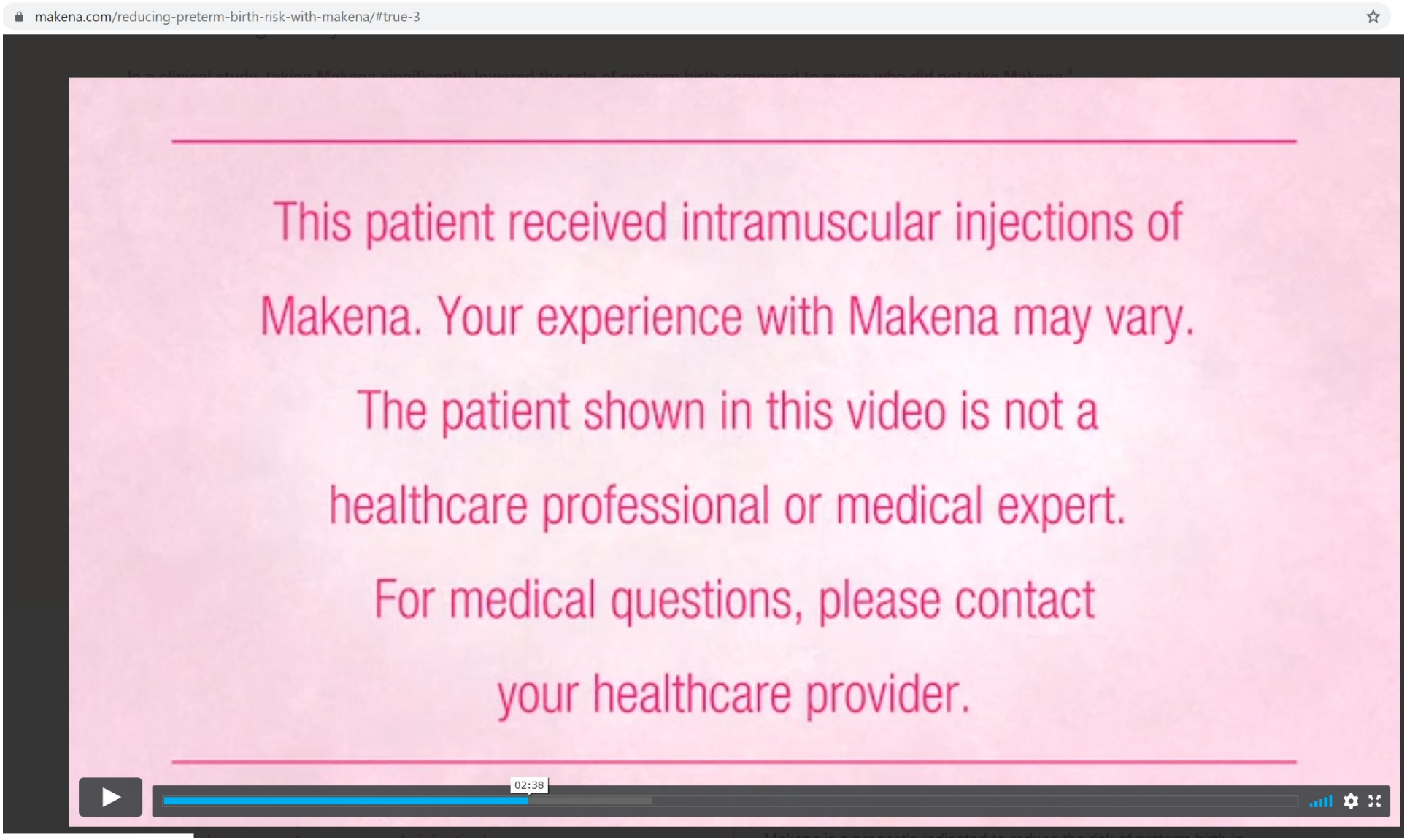
AMAG is committed to continue working with the FDA to determine the best path forward for patients and clinicians.

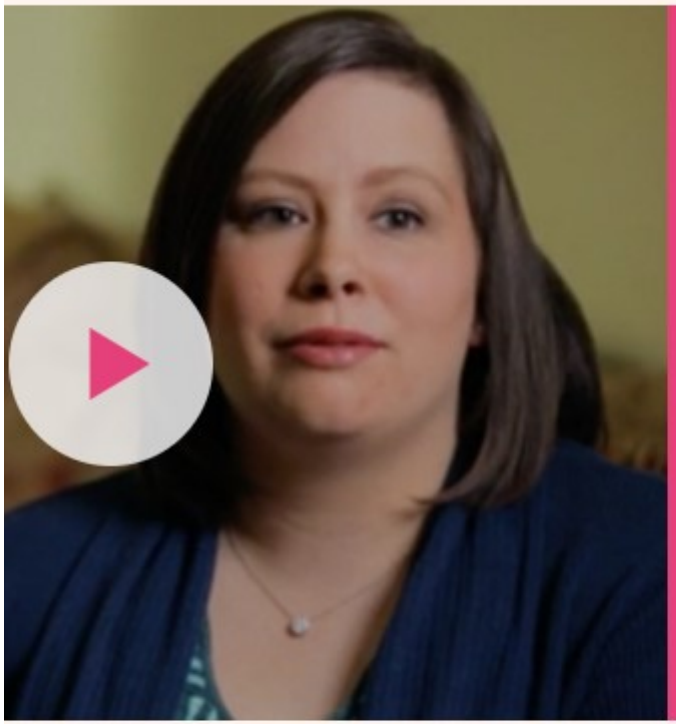
At this time, it is important to know that Makena's approval and product label remain unchanged. Guidelines released on October 25, 2019 regarding 17P are available at: American College of Obstetricians and Gynecologists (https://www.acog.org/Clinical-Guidance-and-Publications/Practice-Advisories/Clinical-guidance-for-integration-of-the-findings-of-The-PROLONG-study-Progestins-Role-in-Optimizing?IsMobileSet=false) *and the Society for*

Maternal-Fetal Medicine (https://www.smfm.org/publications/280-smfm-statement-use-of-17-alpha-hydroxyprogesterone-caproate-for-prevention-of-recurrent-preterm-birth)*. If you have been prescribed or are taking Makena and have questions about your prescription, please speak with your healthcare provider or contact Makena Care Connection® by calling 1-800-847-3418 (M–F, 8AM–8PM ET) or emailing info@makenacareconnection.com* (mailto:info@makenacareconnection.com)*.*

For media questions, please contact corporateaffairs@amagpharma.com (mailto:corporateaffairs@amagpharma.com)*.*

EXHIBIT D


makena.com/reducing-preterm-birth-risk-with-makena/#true-3
This patient received intramuscular injections of Makena. Your experience with Makena may vary. The patient shown in this video is not a healthcare professional or medical expert. For medical questions, please contact your healthcare provider.
02:38



"Looking back, Makena gave me hope that I had a better
delivering Olivia full term."

—Kate, mom of a 35-week preemie

Watch Kate's story (8:10)

EXHIBIT E

IF YOU HAVE HAD A SINGLETON SPONTANEOUS PRETERM BIRTH
(BEFORE 37 WEEKS), YOU ARE AT RISK FOR ANOTHER PRETERM DELIVERY

HELP GIVE YOUR BABY MORE TIME TO DEVELOP

Giving moms an extra layer of personalized support through Makena Care Connection®

Makena®
hydroxyprogesterone
caproate injection

Makena® (hydroxyprogesterone caproate injection) helps give baby more time to develop[1]

Makena is a progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. The effectiveness of Makena is based on improvement in the proportion of women who delivered <37 weeks of gestation. There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity.

Limitation of use: While there are many risk factors for preterm birth, safety and efficacy of Makena has been demonstrated only in women with a prior spontaneous singleton preterm birth. **It is not intended for use in women with multiple gestations or other risk factors for preterm birth.**

Please see **Important Safety Information** on pages 8, 10, and 11 and attached **full Prescribing Information**.

Table of Contents

Makena®
hydroxyprogesterone
caproate injection

What is preterm birth?

The goal of a healthy pregnancy is to deliver full term (39 to 40 weeks) to give your baby the time needed to grow and develop. For example, your baby's brain and lungs are still developing during the last weeks of pregnancy.[2,3]

Preterm birth is when a baby arrives too early; that's before 37 weeks of pregnancy, or 3 weeks prior to the baby's due date.[4] Preterm birth can be unexpected or unplanned. Sometimes, a baby needs to be delivered earlier than normal in certain medical situations.[5]

Preterm birth can happen to any pregnant woman.

In most cases, healthcare providers don't fully understand what actually causes preterm birth. **But moms who have delivered a baby too early (before 37 weeks)—regardless of the number of weeks early they've delivered—in the past are at a higher risk for having another preterm birth.[1,6]**

Every week counts—every additional week makes a difference for your baby. Talk with your healthcare provider about the risks for preterm birth and what you can do to reduce your risk

Have you delivered preterm before?

In the United States, approximately 1 in 10 babies is born prematurely each year.[2] That's nearly 400,000 babies born too early.[7]

Preterm birth rates vary for different racial and ethnic groups. African Americans have a 13.3% preterm birth rate, Native Americans 10.5%, Hispanics 9.1%, Caucasians 8.9%, and Asians 8.5%.[8]

Even if you're healthy and do all the right things during pregnancy, such as maintaining a healthy lifestyle and eating a well-balanced diet, you still could have a premature baby. The good news is there are things you can do to decrease your risk for preterm delivery, especially if you have unexpectedly delivered a baby before 37 weeks of pregnancy in the past.

"My doctor told me that having a previous preterm birth increased my risk of having another preterm baby. My husband and I were very surprised to hear that I was at risk again."

– Lyn, mom of a 36-week preemie

For more Makena mom stories, **visit makena.com**

Please see **Important Safety Information** on pages 8, 10, and 11 and attached **full Prescribing Information**.

Makena®
hydroxyprogesterone caproate injection

Are you aware of the potential risk factors for preterm birth?

The below checklist includes common risk factors for preterm birth.[6] Depending on your risk factor(s), Makena® (hydroxyprogesterone caproate injection) may or may not be right for you.

While there are many causes for preterm birth, the safety and benefits of Makena have been demonstrated only in women who've unexpectedly delivered their baby prior to 37 weeks of pregnancy. **Makena is not meant for use in women with multiple gestations or other risk factors for preterm birth.**

- ☐ Prior spontaneous (unexpected) preterm birth before 37 weeks
- ☐ Pregnant with twins, triplets, or other multiples
- ☐ Problems with the uterus or cervix
- ☐ African American heritage
- ☐ High blood pressure, stress, diabetes, being overweight or underweight
- ☐ Short time between pregnancies (6-18 months)
- ☐ Certain infections during pregnancy, such as an infection of the uterus, vagina, or urinary tract infection, or sexually transmitted disease
- ☐ Smoking, drinking alcohol, or using illegal drugs

You're not alone. If one or more of the above applies to you, **see page 17** of this brochure and talk with your healthcare provider about the risks associated with preterm birth.

Please see **Important Safety Information** on pages 8, 10, and 11 and attached **full Prescribing Information**.

What is Makena?

Makena helps get you closer to term.

Makena, pronounced Ma-keen-a, is a hormone medicine (progestin) prescribed to lower the risk of having another preterm baby in women[1]:

- Who are pregnant with one baby, and
- Who've unexpectedly delivered one baby too early (before 37 weeks) in the past

Makena is a weekly injection (given every 7 days) by your healthcare provider either at their office or in your home.[1]

You can start Makena between 16 weeks and 20 weeks, 6 days of your pregnancy, depending on your healthcare provider's direction.[1]

"My doctor and I discussed the option of taking Makena to reduce my risk of another preterm birth. This gave me peace of mind knowing I was doing everything I could to help give my baby time to develop."

– Sarah, mom of a 34-week preemie

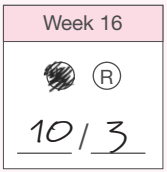
Makena® hydroxyprogesterone caproate injection

Makena® (hydroxyprogesterone caproate injection) therapy schedule

Makena is an injection given by a healthcare provider[1]:

- In the healthcare provider's office or
- At home during a home healthcare visit (if covered by your insurance)

With both Makena injection options, therapy starts between week 16 and week 20, 6 days of your pregnancy, depending on your healthcare provider's direction.[1] You will receive 1 injection each week (every 7 days) until week 37 (your last injection could be as late as 36 weeks, 6 days) or until you deliver your baby, whichever happens first.[1]

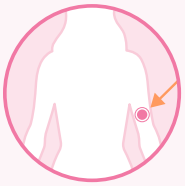


Your Makena Weekly Injection Calendar

To help make Makena part of your routine, **please see pages 18 and 19** for an injection tracker.

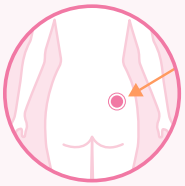
Before you receive Makena, tell your healthcare provider if you have an allergy to hydroxyprogesterone caproate, castor oil, or any of the other ingredients in Makena; diabetes or prediabetes; epilepsy; migraine headaches; asthma; heart problems; kidney problems; depression; or high blood pressure.

Makena administration options



Consider choosing the Makena Auto-Injector[1]:

- Designed so you never see the needle
- Given in the back of the upper arm under the surface of the skin with a shorter, thinner needle
- Full dose delivered in ~15 seconds



Another option is an intramuscular injection[1]:

- Given into your hip (upper outer area of your buttocks) into the muscle with a longer needle
- Full dose delivered over one minute or longer

Whether you choose the Makena Auto-Injector or the intramuscular Makena, you can feel confident that you are getting the same therapy and the opportunity to receive personalized support throughout your pregnancy from Makena Care Connection®[1]

Please see **Important Safety Information** on pages 8, 10, and 11 and attached **full Prescribing Information**.

Makena® hydroxyprogesterone caproate injection

Is Makena® (hydroxyprogesterone caproate injection) safe?

You and your healthcare provider should consider the benefits and risks of therapy with Makena prior to deciding if Makena is right for you.

Makena should not be used if you[1]:

- Have now or have had a history of blood clots or other blood clotting problems
- Have now or have had a history of breast cancer or other hormone-sensitive cancers
- Have unusual vaginal bleeding not related to your current pregnancy
- Have yellowing of your skin due to liver problems during your pregnancy
- Have liver problems, including liver tumors
- Have uncontrolled high blood pressure

Before you receive Makena, tell your healthcare provider if you[1]:

- Have an allergy to hydroxyprogesterone caproate, castor oil, or any of the other ingredients in Makena
- Have diabetes or prediabetes
- Have epilepsy
- Have migraine headaches
- Have asthma
- Have heart problems
- Have kidney problems
- Have depression
- Have high blood pressure

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements

Please see **Important Safety Information** on pages 8, 10, and 11 and attached **full Prescribing Information**.

What are the possible side effects?

For moms: Makena may cause serious side effects, including[1]:

- Blood clots—Symptoms of a blood clot may include leg swelling, redness in your leg, a spot on your leg that is warm to touch, or leg pain that worsens when you bend your foot
- Allergic reactions—Symptoms of an allergic reaction may include hives, itching, or swelling of the face
- Depression
- Yellowing of your skin and the whites of your eyes

The most common side effects of Makena included injection site reactions (pain, swelling, itching, bruising, or a hard bump), hives, itching, nausea, and diarrhea.[1]

In a clinical study, certain complications or events associated with pregnancy occurred more often in women who received Makena. These included miscarriage (pregnancy loss before 20 weeks of pregnancy), stillbirth (fetal death occurring during or after the 20th week of pregnancy), hospital admission for preterm labor, preeclampsia (high blood pressure and too much protein in your urine), gestational hypertension (high blood pressure caused by pregnancy), gestational diabetes, and oligohydramnios (low amniotic fluid levels).[1]

For babies: In a follow-up study, children between the ages of 2 and 5 years old were evaluated for development in various physical, mental, and social measures. The results were comparable to children born to non-Makena-treated moms.[9]

Makena®
hydroxyprogesterone
caproate injection

Makena Care Connection®

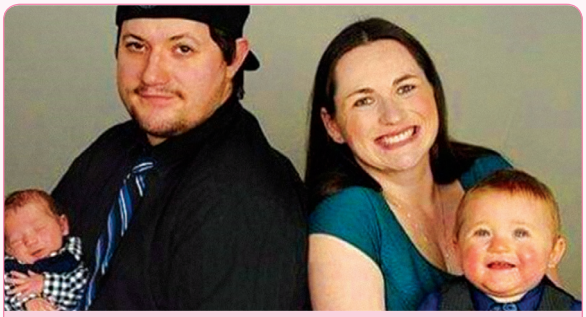
Giving you an extra layer of support with Makena Care Connection®

When you start Makena® (hydroxyprogesterone caproate injection), you get more than the medicine. You get personalized resources that are specifically designed to help you throughout your experience with Makena. Think of us as an extra layer of support.

Prescription Support

Helps you get your prescription approved in a timely manner

You're unique and so are your insurance benefits. Because getting your medicine in a timely manner is important, we're here to lend a hand. We have a dedicated team who understands the coverage policies for Makena. Our experts can handle the details between your healthcare professional, insurance company, and pharmacy so you receive your Makena when you need it.



"It was helpful to lean on Makena Care Connection to help facilitate getting my medication. It was one less thing for me to worry about."

– Amber, mom of a 36-week preemie

Please see **Important Safety Information** on pages 8, 10, and 11 and attached **full Prescribing Information**.

Have Questions? Connect with us.

info@makenacareconnection.com

1-800-847-3418 (M–F, 8AM–8PM ET)

Education & Adherence

Support that helps keep you on track with weekly injections

We understand that moms receiving Makena injections may need some encouragement and support to stick to their weekly injection schedule, and we want to help. This free service offers educational and adherence support to encourage you to make Makena part of your pregnancy and take an active role in your health.

A level of personalized support you can expect:

- Injection reminders that support weekly therapy
- Educational materials to address topics during pregnancy
- Encouragement so you can take an active role in your health

"Knowing my Care Manager was just a phone call away gave me peace of mind. I appreciated feeling like I had someone supporting me every step of the way."

– Shanise, mom of a 22-week preemie

Makena® hydroxyprogesterone caproate injection

Financial Assistance

Helps ensure affordable access to Makena® (hydroxyprogesterone caproate injection)

We believe that you should be able to focus on your pregnancy more than the cost of your medication. To support that, AMAG Pharmaceuticals is committed to making sure that Makena-eligible moms have affordable access to Makena. We offer eligible patients* financial assistance.

Commercially insured moms whose health plan covers Makena

- Helps lower out-of-pocket costs associated with copays, coinsurance, and deductibles*

Uninsured and commercially underinsured moms

- A free course of therapy*

"I was so happy that I was approved for financial assistance. I feel very thankful that my family and I had this opportunity with the Makena Care Connection."

– Nalleli, mom of a 36-week preemie

For more Makena mom stories, **visit makena.com**

Home Injections by Healthcare Professionals

Provides injection administration in the comfort of your home

We can help coordinate Makena injections through a home healthcare organization. Once you're approved by insurance, you can choose to receive your injections by a healthcare professional in the comfort of your home or another location that's convenient for you.

*Each patient's eligibility is evaluated on an individual basis. To be eligible, patients must meet the FDA-approved indication (pregnant with a single baby, with a history of singleton spontaneous preterm birth <37 weeks).[1] In compliance with federal regulations, patients insured by a government-funded program (eg, Medicaid, TRICARE, etc) are not eligible. There are no upper-level income caps.

Please see **Important Safety Information** on pages 8, 10, and 11 and attached **full Prescribing Information**.

Makena® hydroxyprogesterone caproate injection

Is Makena® (hydroxyprogesterone caproate injection) right for you?

In a clinical study, taking Makena significantly lowered the rate of preterm birth compared to moms who did not take Makena.[1]

If you answer "yes" to all of the questions below, talk with your healthcare provider to see if Makena is right for you to reduce your risk of another preterm birth.

- ☐ Have you unexpectedly delivered a baby preterm (less than 37 weeks gestation, or more than 3 weeks too early) before?
- ☐ Was your preterm birth due to preterm labor or your water breaking?
- ☐ Are you currently pregnant with one baby?

While there are many causes for preterm birth, the safety and benefits of Makena have been demonstrated only in women who've unexpectedly delivered their baby prior to 37 weeks of pregnancy.

Makena is not meant for use in women with multiple gestations or other risk factors for preterm birth.

If you think you are at risk for another preterm birth due to a history of spontaneous preterm birth, ask if Makena may be right for you

Please see **Important Safety Information** on pages 8, 10 and 11 and attached **full Prescribing Information.**

Questions to ask your healthcare provider

Here are some questions to help you start a conversation about your prior preterm birth experience and how Makena may be able to help reduce your risk of another preterm birth.

Ask your healthcare provider these questions to see if Makena is right for you:

- I delivered a baby unexpectedly before 37 weeks. Could this happen again?
- What are some of the risk factors for preterm birth?
- How can I reduce my risk and have a better chance for a full-term pregnancy?
- How early could I go into labor?
- What are the signs and symptoms of preterm labor?
- Is Makena right for me?

References: 1. Makena® (hydroxyprogesterone caproate injection) prescribing information, AMAG Pharmaceuticals, 2018. **2.** Long-term health effects of premature birth. March of Dimes website. https://www.marchofdimes.org/complications/long-term-health-effects-of-premature-birth.aspx. Last reviewed October 2013. Accessed November 14, 2017. **3.** American College of Obstetricians and Gynecologists Committee on Obstetric Practice Society for Maternal-Fetal Medicine. Committee opinion 579: Definition of term pregnancy. *Obstet Gynecol*. 2013;122(5):1139-1140. **4.** Preterm (premature) labor and birth. American College of Obstetricians and Gynecologists website. https://www.acog.org/-/media/For-Patients/faq087.pdf. November 2016. Accessed October 12, 2017. **5.** Why at least 39 weeks is best for your baby. March of Dimes website. https://www.marchofdimes.org/pregnancy/why-at-least-39-weeks-is-best-for-your-baby.aspx. Last reviewed September 2013. Accessed February 21, 2018. **6.** Preterm Labor and Preterm Birth. March of Dimes website. https://www.marchofdimes.org/pregnancy/preterm-labor-and-premature-birth.aspx. Last reviewed October 2014. Accessed October 12, 2017. **7.** Prematurity research. March of Dimes website. https://www.marchofdimes.org/research/prematurity-research.aspx. Accessed October 12, 2017. **8.** March of Dimes 2017 Premature Birth Report Card. March of Dimes website. https://www.marchofdimes.org/materials/PrematureBirthReportCard-United-States-2017.pdf. **9.** Northen AT, Norman GS, Anderson K, et al. Follow-up of children exposed in utero to 17 α-hydroxyprogesterone caproate compared with placebo. *Obstet Gynecol*. 2007;110(4):865-872.

Makena®
hydroxyprogesterone
caproate injection

Make Makena a part of your weekly routine!

Use this calendar as a resource to track your weekly injections

A Makena is administered once weekly (every 7 days) by your healthcare provider, between 16 weeks and 20 weeks, 6 days, continuing until 37 weeks (your last injection could be as late as 36 weeks, 6 days) or until you deliver your baby, whichever happens first.[1]

B Each week you receive your injection, your healthcare provider will rotate the injection site from the previous side.[1] You'll be able to keep track of this on the calendar too!

C Set a day to make your Makena injections part of your weekly routine.

Please note that your results and duration of therapy may vary.

My Makena injection is every _____

SECOND TRIMESTER			
Week 16	Week 17	Week 18	Week 19
Ⓛ Ⓡ ___/___	Ⓛ Ⓡ ___/___	Ⓛ Ⓡ ___/___	Ⓛ Ⓡ ___/___
Week 20	Week 21	Week 22	Week 23
Ⓛ Ⓡ ___/___	Ⓛ Ⓡ ___/___	Ⓛ Ⓡ ___/___	Ⓛ Ⓡ ___/___
Week 24	Week 25	Week 26	Week 27
Ⓛ Ⓡ ___/___	Ⓛ Ⓡ ___/___	Ⓛ Ⓡ ___/___	Ⓛ Ⓡ ___/___

THIRD TRIMESTER			
Week 28	Week 29	Week 30	Week 31
Ⓛ Ⓡ ___/___	Ⓛ Ⓡ ___/___	Ⓛ Ⓡ ___/___	Ⓛ Ⓡ ___/___
Week 32	Week 33	Week 34	Week 35
Ⓛ Ⓡ ___/___	Ⓛ Ⓡ ___/___	Ⓛ Ⓡ ___/___	Ⓛ Ⓡ ___/___
Week 36			
Ⓛ Ⓡ ___/___			

Weeks 37-38
This is early term, and baby is still growing[3]

Weeks 39-40
This is full term—the goal of a healthy pregnancy[3]

Please see **Important Safety Information** on pages 8, 10 and 11 and attached **full Prescribing Information.**

Makena® hydroxyprogesterone caproate injection

IF YOU HAVE HAD A SINGLETON SPONTANEOUS PRETERM BIRTH (BEFORE 37 WEEKS), YOU ARE AT RISK FOR ANOTHER PRETERM DELIVERY

Every week counts when you're pregnant

Your baby keeps growing and developing every week of pregnancy until your due date.[2,4]

Together, you and your healthcare provider can take an important step to help give your baby more time to develop.

Ask your healthcare provider about the importance of having a full-term delivery.

Have Questions? Connect with us.

1-800-847-3418 (M–F, 8AM–8PM ET)

Full Prescribing Information attached here.

If missing, please visit **http://www.makena.com/pi**

Please see **Important Safety Information** on pages 8, 10, and 11 and attached **full Prescribing Information**.

Marketed by AMAG Pharmaceuticals, Inc. Waltham, MA, 02451

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MAKENA safely and effectively. See full prescribing information for MAKENA.

MAKENA® (hydroxyprogesterone caproate injection) for intramuscular or subcutaneous use.

Initial U.S. Approval: 1956

RECENT MAJOR CHANGES

Dosage and Administration, Dosing (2.1)	02/2018
Dosage and Administration, Preparation & Administration (2.2)	02/2018

INDICATIONS AND USAGE

Makena is a progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth (1). The effectiveness of Makena is based on improvement in the proportion of women who delivered < 37 weeks of gestation (14). There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity.

Limitation of use: Makena is not intended for use in women with multiple gestations or other risk factors for preterm birth. (1)

DOSAGE AND ADMINISTRATION

- Makena auto-injector: Administer subcutaneously using Makena auto-injector at a dose of 275 mg (1.1 mL) once weekly, in the back of either upper arm (2.1)
- Makena (single- and multi-dose vials): Administer intramuscularly at a dose of 250 mg (1 mL) once weekly in the upper outer quadrant of the gluteus maximus (2.1)
- Begin treatment between 16 weeks, 0 days and 20 weeks, 6 days of gestation (2.1)
- Continue administration once weekly until week 37 (through 36 weeks, 6 days) of gestation or delivery, whichever occurs first (2.1)

DOSAGE FORMS AND STRENGTHS

1.1 mL single-use auto-injector for subcutaneous use contains 275 mg of hydroxyprogesterone caproate (250 mg/mL) (3)

1 mL single-dose vial for intramuscular use contains 250 mg of hydroxyprogesterone caproate. (3)

5 mL multi-dose vial for intramuscular use contains 1250 mg of hydroxyprogesterone caproate (250 mg/mL). (3)

CONTRAINDICATIONS

- Current or history of thrombosis or thromboembolic disorders (4)
- Known or suspected breast cancer, other hormone-sensitive cancer, or history of these conditions (4)
- Undiagnosed abnormal vaginal bleeding unrelated to pregnancy (4)
- Cholestatic jaundice of pregnancy (4)
- Liver tumors, benign or malignant, or active liver disease (4)
- Uncontrolled hypertension (4)

WARNINGS AND PRECAUTIONS

- Thromboembolic disorders: Discontinue if thrombosis or thromboembolism occurs (5.1)
- Allergic reactions: Consider discontinuing if allergic reactions occur (5.2)
- Decreased glucose tolerance: Monitor prediabetic and diabetic women receiving Makena (5.3)
- Fluid retention: Monitor women with conditions that may be affected by fluid retention, such as preeclampsia, epilepsy, cardiac or renal dysfunction (5.4)
- Depression: Monitor women with a history of clinical depression; discontinue Makena if depression recurs (5.5)

ADVERSE REACTIONS

- In a study where the Makena intramuscular injection was compared with placebo, the most common adverse reactions reported with Makena intramuscular injection (reported incidence in ≥ 2% of subjects and higher than in the control group) were: injection site reactions (pain [35%], swelling [17%], pruritus [6%], nodule [5%]), urticaria (12%), pruritus (8%), nausea (6%), and diarrhea (2%). (6.1)
- In studies where the Makena subcutaneous injection using auto-injector was compared with Makena intramuscular injection, the most common adverse reaction reported with Makena auto-injector use (and higher than with Makena intramuscular injection) was injection site pain (10% in one study and 34% in another). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AMAG Pharmaceuticals at 1-877-411-2510 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised 02/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Makena is a progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. The effectiveness of Makena is based on improvement in the proportion of women who delivered < 37 weeks of gestation. There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity.

Limitation of use: While there are many risk factors for preterm birth, safety and efficacy of Makena has been demonstrated only in women with a prior spontaneous singleton preterm birth. **It is not intended for use in women with multiple gestations or other risk factors for preterm birth.**

2 DOSAGE AND ADMINISTRATION

2.1 Dosing

- Makena auto-injector: Administer **subcutaneously** using auto-injector at a dose of 275 mg (1.1 mL) once weekly (every 7 days) in the back of either upper arm by a healthcare provider
- Makena (single- and multi-dose vials): Administer **intramuscularly** at a dose of 250 mg (1 mL) once weekly (every 7 days) in the upper outer quadrant of the gluteus maximus by a healthcare provider
- Begin treatment between 16 weeks, 0 days and 20 weeks, 6 days of gestation
- Continue administration once weekly until week 37 (through 36 weeks, 6 days) of gestation or delivery, whichever occurs first

2.2 Preparation and Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Makena is a clear, yellow solution. The solution must be clear at the time of use; replace vial if visible particles or crystals are present.

Specific instructions for administration by dosage form:

Makena single-dose or multi-dose vials (intramuscular use only)

Makena single-dose or multi-dose vials are only for intramuscular injection with a syringe into the upper outer quadrant of the gluteus maximus, rotating the injection site to the alternate side from the previous week, using the following preparation and administration procedure:

1. Clean the vial top with an alcohol swab before use.
2. Draw up 1 mL of drug into a 3 mL syringe with an 18 gauge needle.
3. Change the needle to a 21 gauge 1½ inch needle.
4. After preparing the skin, inject in the upper outer quadrant of the gluteus maximus. The solution is viscous and oily. Slow injection (over one minute or longer) is recommended.
5. Applying pressure to the injection site may minimize bruising and swelling.

If the 5 mL multi-dose vial is used, discard any unused product 5 weeks after first use.

Makena auto-injector (subcutaneous use only)

Makena auto-injector is a single-use, pre-filled, disposable device containing a 27 gauge, 0.5 inch needle that delivers one dose subcutaneously in the back of the upper arm.

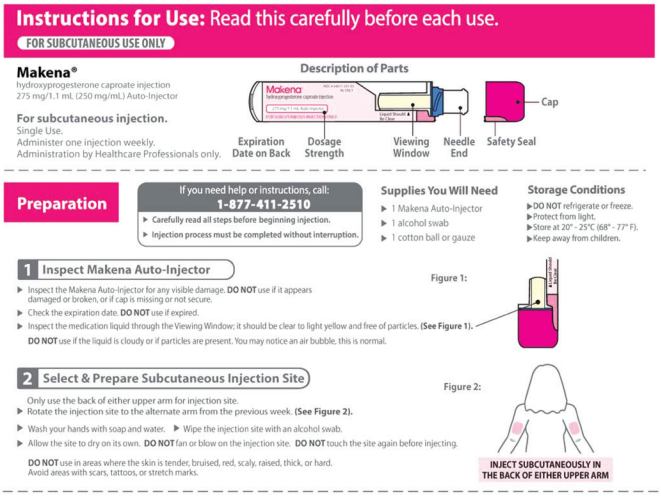
Because Makena auto-injector is preservative-free, once the cap is removed the device should be used immediately or discarded.

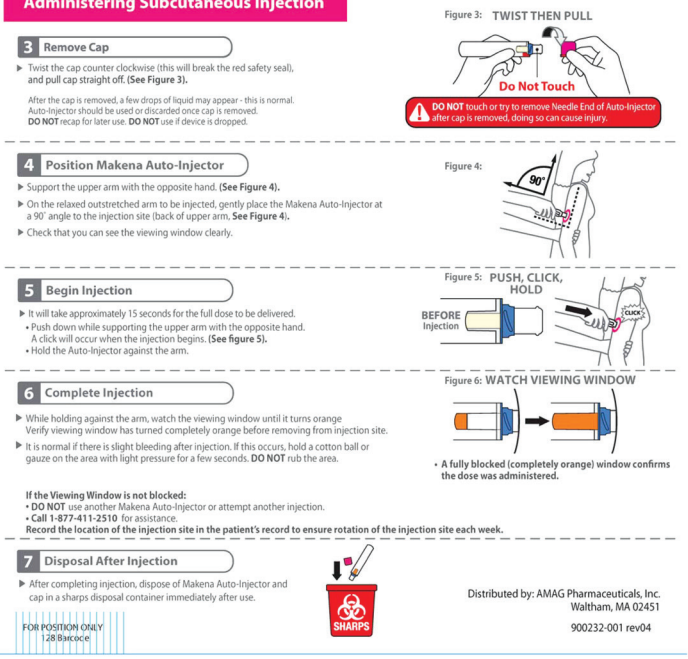
Rotate the injection site to the alternate arm from the previous week. Do not use in areas where the skin is tender, bruised, red, scaly, raised, thick, or hard. Avoid areas with scars, tattoos, or stretch marks.

The solution is viscous and oily. The auto-injector takes approximately 15 seconds to deliver the dose; when the viewing window is fully blocked (completely orange), the full dose has been administered.

The "Instructions for Use" contains detailed steps for administering the subcutaneous injection using the auto-injector [*see Dosage and Administration (2.3)*]. Read the "Instructions for Use" carefully before administering Makena auto-injector.

2.3 Instructions for Use (Makena Auto-injector)





3 DOSAGE FORMS AND STRENGTHS

Subcutaneous injection: 275 mg/1.1 mL clear yellow solution in single-use auto-injector.
Intramuscular injection: 250 mg/mL clear yellow solution in single-dose vials.
Intramuscular injection: 1250 mg/5 mL (250 mg/mL) clear yellow solution in multiple-dose vials.

4 CONTRAINDICATIONS

Do not use Makena in women with any of the following conditions:

- Current or history of thrombosis or thromboembolic disorders
- Known or suspected breast cancer, other hormone-sensitive cancer, or history of these conditions
- Undiagnosed abnormal vaginal bleeding unrelated to pregnancy
- Cholestatic jaundice of pregnancy
- Liver tumors, benign or malignant, or active liver disease
- Uncontrolled hypertension

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders

Discontinue Makena if an arterial or deep venous thrombotic or thromboembolic event occurs.

5.2 Allergic Reactions

Allergic reactions, including urticaria, pruritus and angioedema, have been reported with use of Makena or with other products containing castor oil. Consider discontinuing the drug if such reactions occur.

5.3 Decrease in Glucose Tolerance

A decrease in glucose tolerance has been observed in some patients on progestin treatment. The mechanism of this decrease is not known. Carefully monitor prediabetic and diabetic women while they are receiving Makena.

5.4 Fluid Retention

Because progestational drugs may cause some degree of fluid retention, carefully monitor women with conditions that might be influenced by this effect (e.g., preeclampsia, epilepsy, migraine, asthma, cardiac or renal dysfunction).

5.5 Depression

Monitor women who have a history of clinical depression and discontinue Makena if clinical depression recurs.

5.6 Jaundice

Carefully monitor women who develop jaundice while receiving Makena and consider whether the benefit of use warrants continuation.

5.7 Hypertension

Carefully monitor women who develop hypertension while receiving Makena and consider whether the benefit of use warrants continuation.

6 ADVERSE REACTIONS

For the most serious adverse reactions to the use of progestins, see *Warnings and Precautions (5)*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in practice.
In a vehicle (placebo)-controlled clinical trial of 463 pregnant women at risk for spontaneous preterm delivery based on obstetrical history, 310 received 250 mg of Makena and 153 received a vehicle formulation containing no drug by a weekly intramuscular injection beginning at 16 to 20 weeks of gestation and continuing until 37 weeks of gestation or delivery, whichever occurred first. [*See Clinical Studies (14.1)*.]

Certain pregnancy-related fetal and maternal complications or events were numerically increased in the Makena-treated subjects as compared to control subjects, including miscarriage and stillbirth, admission for preterm labor, preeclampsia or gestational hypertension, gestational diabetes, and oligohydramnios (Tables 1 and 2).

Table 1 Selected Fetal Complications

Pregnancy Complication	Makena n/N	Control n/N
Miscarriage (< 20 weeks)[1]	5/209	0/107
Stillbirth (≥ 20 weeks)[2]	6/305	2/153

[1] N = Total number of subjects enrolled prior to 20 weeks 0 days
[2] N = Total number of subjects at risk ≥ 20 weeks

Table 2 Selected Maternal Complications

Pregnancy Complication	Makena N=310 %	Control N=153 %
Admission for preterm labor[1]	16.0	13.8
Preeclampsia or gestational hypertension	8.8	4.6
Gestational diabetes	5.6	4.6
Oligohydramnios	3.6	1.3

[1] Other than delivery admission.

Common Adverse Reactions:
The most common adverse reaction with intramuscular injection was injection site pain, which was reported after at least one injection by 34.8% of the Makena group and 32.7% of the control group. Table 3 lists adverse reactions that occurred in ≥ 2% of subjects and at a higher rate in the Makena group than in the control group.

Table 3 Adverse Reactions (Occurring at ≥ 2% of Makena-Treated Subjects and at a Higher Rate than Control Subjects

Preferred Term	Makena N=310 %	Control N=153 %
Injection site pain	34.8	32.7
Injection site swelling	17.1	7.8
Urticaria	12.3	11.1
Pruritus	7.7	5.9
Injection site pruritus	5.8	3.3
Nausea	5.8	4.6
Injection site nodule	4.5	2.0
Diarrhea	2.3	0.7

In the clinical trial using intramuscular injection, 2.2% of subjects receiving Makena were reported as discontinuing therapy due to adverse reactions compared to 2.6% of control subjects. The most common adverse reactions that led to discontinuation in both groups were urticaria and injection site pain/swelling (1% each).

Pulmonary embolus in one subject and injection site cellulitis in another subject were reported as serious adverse reactions in Makena-treated subjects.

Two clinical studies were conducted in healthy post-menopausal women, comparing Makena administered via subcutaneous auto-injector to Makena administered as an intramuscular injection. In the first study, injection site pain occurred in 3/30 (10%) of subjects who used the subcutaneous auto-injector vs. 2/30 (7%) of subjects receiving intramuscular injection. In the second study, injection site pain occurred in 20/59 (34%) of subjects who used the subcutaneous auto-injector vs. 5/61 (8%) of subjects receiving intramuscular injection.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Makena. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Body as a whole*: Local injection site reactions (including erythema, urticaria, rash, irritation, hypersensitivity, warmth); fatigue; fever; hot flashes/flushes
- *Digestive disorders*: Vomiting
- *Infections*: Urinary tract infection
- *Nervous system disorders*: Headache, dizziness
- *Pregnancy, puerperium and perinatal conditions:* Cervical incompetence, premature rupture of membranes
- *Reproductive system and breast disorders:* Cervical dilation, shortened cervix
- *Respiratory disorders*: Dyspnea, chest discomfort
- *Skin*: Rash

7 DRUG INTERACTIONS

In vitro drug-drug interaction studies were conducted with Makena. Hydroxyprogesterone caproate has minimal potential for CYP1A2, CYP2A6, and CYP2B6 related drug-drug interactions at the clinically relevant concentrations. *In vitro* data indicated that therapeutic concentration of hydroxyprogesterone caproate is not likely to inhibit the activity of CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 [*See Clinical Pharmacology (12.3)*.] No *in vivo* drug-drug interaction studies were conducted with Makena.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
Makena is indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. Fetal, neonatal, and maternal risks are discussed throughout labeling. Data from the placebo-controlled clinical trial and the infant follow-up safety study [*see Clinical Studies (14.1, 14.2)*] did not show a difference in adverse developmental outcomes between children of Makena-treated women and children of control subjects. However, these data are insufficient to determine a drug-associated risk of adverse developmental outcomes as none of the Makena-treated women received the drug during the first trimester of pregnancy. In animal reproduction studies, intramuscular administration of hydroxyprogesterone caproate to pregnant rats during gestation at doses 5 times the human dose equivalent based on a 60-kg human was not associated with adverse developmental outcomes.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data
Animal Data
Reproduction studies of hydroxyprogesterone caproate administered to various animal species have been reported in the literature. In nonhuman primates, embryolethality was reported in rhesus monkeys administered hydroxyprogesterone caproate up to 2.4 and 24 times the human dose equivalent, but not in cynomolgus monkeys administered hydroxyprogesterone caproate at doses up to 2.4 times the human dose equivalent, every 7 days between days 20 and 146 of gestation. There were no teratogenic effects in either strain of monkey.

Reproduction studies have been performed in mice and rats at doses up to 95 and 5, respectively, times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to hydroxyprogesterone caproate.

8.2 Lactation

Risk Summary
Low levels of progestins are present in human milk with the use of progestin-containing products, including hydroxyprogesterone caproate. Published studies have reported no adverse effects of progestins on the breastfed child or on milk production.

8.4 Pediatric Use

Makena is not indicated for use in women under 16 years of age. Safety and effectiveness in patients less than 16 years of age have not been established. A small number of women under age 18 years were studied; safety and efficacy are expected to be the same in women aged 16 years and above as for users 18 years and older [*see Clinical Studies (14)*].

8.6 Hepatic Impairment

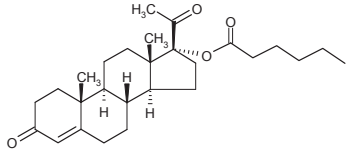
No studies have been conducted to examine the pharmacokinetics of Makena in patients with hepatic impairment. Makena is extensively metabolized and hepatic impairment may reduce the elimination of Makena.

10 OVERDOSAGE

There have been no reports of adverse events associated with overdosage of Makena in clinical trials. In the case of overdosage, the patient should be treated symptomatically.

11 DESCRIPTION

The active pharmaceutical ingredient in Makena is hydroxyprogesterone caproate, a progestin.
The chemical name for hydroxyprogesterone caproate is pregn-4-ene-3,20-dione, 17[(1-oxohexyl) oxy]. It has an empirical formula of $C_{27}H_{40}O_4$ and a molecular weight of 428.60. Hydroxyprogesterone caproate exists as white to practically white crystals or powder with a melting point of 120°-124°C.
The structural formula is:



Makena is a clear, yellow, sterile, non-pyrogenic solution for intramuscular (vials) or subcutaneous (auto-injector) injection. Each 1.1 mL Makena auto-injector for subcutaneous use and each 1 mL single-dose vial for intramuscular use contains hydroxyprogesterone caproate USP, 250 mg/mL (25% w/v), in a preservative-free solution containing castor oil USP (30.6% v/v) and benzyl benzoate USP (46% v/v). Each 5 mL multi-dose vial contains hydroxyprogesterone caproate USP, 250 mg/mL (25% w/v), in castor oil USP (28.6%) and benzyl benzoate USP (46% v/v) with the preservative benzyl alcohol NF (2% v/v).

12 **CLINICAL PHARMACOLOGY**

12.1 Mechanism of Action

Hydroxyprogesterone caproate is a synthetic progestin. The mechanism by which hydroxyprogesterone caproate reduces the risk of recurrent preterm birth is not known.

12.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted with Makena.

12.3 Pharmacokinetics

Absorption: Female patients with a singleton pregnancy received intramuscular doses of 250 mg hydroxyprogesterone caproate for the reduction of preterm birth starting between 16 weeks 0 days and 20 weeks 6 days. All patients had blood drawn daily for 7 days to evaluate pharmacokinetics.

Table 4 Summary of Mean (Standard Deviation) Pharmacokinetic Parameters for Hydroxyprogesterone Caproate

Group (N)	C_{max} (ng/mL)	T_{max} (days)[a]	$AUC_{(0-t)}$[b] (ng·hr/mL)
Group 1 (N=6)	5.0 (1.5)	5.5 (2.0-7.0)	571.4 (195.2)
Group 2 (N=8)	12.5 (3.9)	1.0 (0.9-1.9)	1269.6 (285.0)
Group 3 (N=11)	12.3 (4.9)	2.0 (1.0-3.0)	1268.0 (511.6)

Blood was drawn daily for 7 days (1) starting 24 hours after the first dose between Weeks 16-20 (Group 1), (2) after a dose between Weeks 24-28 (Group 2), or (3) after a dose between Weeks 32-36 (Group 3)

[a] Reported as median (range)

[b] t = 7 days

For all three groups, peak concentration (C_{max}) and area under the curve ($AUC_{(1-7\ days)}$) of the mono-hydroxylated metabolites were approximately 3-8-fold lower than the respective parameters for the parent drug, hydroxyprogesterone caproate. While di-hydroxylated and tri-hydroxylated metabolites were also detected in human plasma to a lesser extent, no meaningful quantitative results could be derived due to the absence of reference standards for these multiple hydroxylated metabolites. The relative activity and significance of these metabolites are not known.

The elimination half-life of hydroxyprogesterone caproate, as evaluated from 4 patients in the study who reached full-term in their pregnancies, was 16.4 (±3.6) days. The elimination half-life of the mono-hydroxylated metabolites was 19.7 (±6.2) days.

In a single-dose, open-label, randomized, parallel design bioavailability study in 120 healthy post-menopausal women, comparable systemic exposure of hydroxyprogesterone caproate was seen when Makena was administered subcutaneously with the auto-injector (1.1 mL) in the back of the upper arm and when Makena was dosed intramuscularly (1 mL) in the upper outer quadrant of the gluteus maximus.

Distribution: Hydroxyprogesterone caproate binds extensively to plasma proteins including albumin and corticosteroid binding globulins.

Metabolism: In vitro studies have shown that hydroxyprogesterone caproate can be metabolized by human hepatocytes, both by phase I and phase II reactions. Hydroxyprogesterone caproate undergoes extensive reduction, hydroxylation and conjugation. The conjugated metabolites include sulfated, glucuronidated and acetylated products. In vitro data indicate that the metabolism of hydroxyprogesterone caproate is predominantly mediated by CYP3A4 and CYP3A5. The in vitro data indicate that the caproate group is retained during metabolism of hydroxyprogesterone caproate.

Excretion: Both conjugated metabolites and free steroids are excreted in the urine and feces, with the conjugated metabolites being prominent. Following intramuscular administration to pregnant women at 10-12 weeks gestation, approximately 50% of a dose was recovered in the feces and approximately 30% recovered in the urine.

Drug Interactions

Cytochrome P450 (CYP) enzymes: An *in vitro* inhibition study using human liver microsomes and CYP isoform-selective substrates indicated that hydroxyprogesterone caproate increased the metabolic rate of CYP1A2, CYP2A6, and CYP2B6 by approximately 80%, 150%, and 80%, respectively. However, in another *in vitro* study using human hepatocytes under conditions where the prototypical inducers or inhibitors caused the anticipated increases or decreases in CYP enzyme activities, hydroxyprogesterone caproate did not induce or inhibit CYP1A2, CYP2A6, or CYP2B6 activity. Overall, the findings indicate that hydroxyprogesterone caproate has minimal potential for CYP1A2, CYP2A6, and CYP2B6 related drug-drug interactions at the clinically relevant concentrations.

In vitro data indicated that therapeutic concentration of hydroxyprogesterone caproate is not likely to inhibit the activity of CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4.

13 **NONCLINICAL TOXICOLOGY**

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Hydroxyprogesterone caproate has not been adequately evaluated for carcinogenicity.

No reproductive or developmental toxicity or impaired fertility was observed in a multigenerational study in rats. Hydroxyprogesterone caproate administered intramuscularly, at gestational exposures up to 5 times the recommended human dose, had no adverse effects on the parental (F_0) dams, their developing offspring (F_1), or the latter offspring's ability to produce a viable, normal second (F_2) generation.

14 **CLINICAL STUDIES**

14.1 Clinical Trial to Evaluate Reduction of Risk of Preterm Birth

In a multicenter, randomized, double-blind, vehicle (placebo)-controlled clinical trial, the safety and effectiveness of Makena for the reduction of the risk of spontaneous preterm birth was studied in women with a singleton pregnancy (age 16 to 43 years) who had a documented history of singleton spontaneous preterm birth (defined as delivery at less than 37 weeks of gestation following spontaneous preterm labor or premature rupture of membranes). At the time of randomization (between 16 weeks, 0 days and 20 weeks, 6 days of gestation), an ultrasound examination had confirmed gestational age and no known fetal anomaly. Women were excluded for prior progesterone treatment or heparin therapy during the current pregnancy, a history of thromboembolic disease, or maternal/obstetrical complications (such as current or planned cerclage, hypertension requiring medication, or a seizure disorder).

A total of 463 pregnant women were randomized to receive either Makena (N=310) or vehicle (N=153) at a dose of 250 mg administered weekly by intramuscular injection starting between 16 weeks, 0 days and 20 weeks, 6 days of gestation, and continuing until 37 weeks of gestation or delivery. Demographics of the Makena-treated women were similar to those in the control group, and included: 59.0% Black, 25.5% Caucasian, 13.9% Hispanic and 0.6% Asian. The mean body mass index was 26.9 kg/m^2.

The proportions of women in each treatment arm who delivered at < 37 (the primary study endpoint), < 35, and < 32 weeks of gestation are displayed in Table 5.

Table 5 Proportion of Subjects Delivering at < 37, < 35 and < 32 Weeks Gestational Age (ITT Population)

Delivery Outcome	Makena[1] (N=310) %	Control (N=153) %	Treatment difference and 95% Confidence Interval[2]
<37 weeks	37.1	54.9	-17.8% [-28.0%, -7.4%]
<35 weeks	21.3	30.7	-9.4% [-19.0%, -0.4%]
<32 weeks	11.9	19.6	-7.7% [-16.1%, -0.3%]

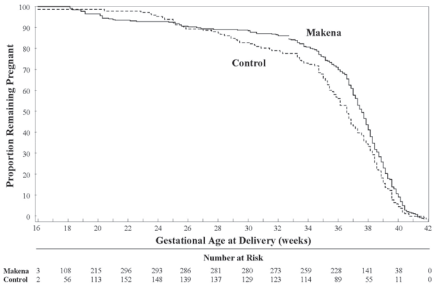
[1] Four Makena-treated subjects were lost to follow-up. They were counted as deliveries at their gestational ages at time of last contact (18^4, 22^0, 34^3 and 36^4 weeks).

[2] Adjusted for interim analysis.

Compared to controls, treatment with Makena reduced the proportion of women who delivered preterm at < 37 weeks. The proportions of women delivering at < 35 and < 32 weeks also were lower among women treated with Makena. The upper bounds of the confidence intervals for the treatment difference at < 35 and < 32 weeks were close to zero. Inclusion of zero in a confidence interval would indicate the treatment difference is not statistically significant. Compared to the other gestational ages evaluated, the number of preterm births at < 32 weeks was limited.

After adjusting for time in the study, 7.8% of Makena-treated subjects delivered prior to 25 weeks compared to 4.7% of control subjects, see Figure 1.

Figure 1 Proportion of Women Remaining Pregnant as a Function of Gestational Age



The rates of fetal losses and neonatal deaths in each treatment arm are displayed in Table 6. Due to the higher rate of miscarriages and stillbirths in the Makena arm, there was no overall survival difference demonstrated in this clinical trial.

Table 6 Fetal Losses and Neonatal Deaths

Complication	Makena N=306[A] n (%)[B]	Control N=153 n (%)[B]
Miscarriages <20 weeks gestation[C]	5 (2.4)	0
Stillbirth	6 (2.0)	2 (1.3)
Antepartum stillbirth	*5 (1.6)*	*1 (0.6)*
Intrapartum stillbirth	*1 (0.3)*	*1 (0.6)*
Neonatal deaths	8 (2.6)	9 (5.9)
Total Deaths	**19 (6.2)**	**11 (7.2)**

[A] Four of the 310 Makena-treated subjects were lost to follow-up and stillbirth or neonatal status could not be determined

[B] Percentages are based on the number of enrolled subjects and not adjusted for time on drug

[C] Percentage adjusted for the number of at risk subjects (n=209 for Makena, n=107 for control) enrolled at <20 weeks gestation.

A composite neonatal morbidity/mortality index evaluated adverse outcomes in live births. It was based on the number of neonates who died or experienced respiratory distress syndrome, bronchopulmonary dysplasia, grade 3 or 4 intraventricular hemorrhage, proven sepsis, or necrotizing enterocolitis. Although the proportion of neonates who experienced 1 or more events was numerically lower in the Makena arm (11.9% vs. 17.2%), the number of adverse outcomes was limited and the difference between arms was not statistically significant.

14.2 Infant Follow-Up Safety Study

Infants born to women enrolled in this study, and who survived to be discharged from the nursery, were eligible for participation in a follow-up safety study. Of 348 eligible offspring, 79.9% enrolled: 194 children of Makena-treated women and 84 children of control subjects. The primary endpoint was the score on the Ages & Stages Questionnaire (ASQ), which evaluates communication, gross motor, fine motor, problem solving, and personal/social parameters. The proportion of children whose scores met the screening threshold for developmental delay in each developmental domain was similar for each treatment group.

16 **HOW SUPPLIED/STORAGE AND HANDLING**

Makena auto-injector (for subcutaneous injection)

Makena auto-injector (NDC 64011-301-03) is supplied as 1.1 mL of a clear yellow sterile preservative-free solution in an auto-injector containing a pre-filled syringe. Each 1.1 mL auto-injector contains hydroxyprogesterone caproate USP, 250 mg/mL (25% w/v), in castor oil USP (30.6% v/v) and benzyl benzoate USP (46% v/v).

Single unit carton: Contains one 1.1 mL single-patient-use auto-injector of Makena containing 275 mg of hydroxyprogesterone caproate.

Store at 20° to 25°C (68° to 77°F). Do not refrigerate or freeze.

Caution: Protect auto-injector from light. Store auto-injector in its box.

Makena single- and multi-dose vials (for intramuscular injection)

Makena (NDC 64011-247-02) is supplied as 1 mL of a sterile preservative-free clear yellow solution in a single-dose glass vial.

Each 1 mL vial contains hydroxyprogesterone caproate USP, 250 mg/mL (25% w/v), in castor oil USP (30.6% v/v) and benzyl benzoate USP (46% v/v).

Single unit carton: Contains one 1 mL single-dose vial of Makena containing 250 mg of hydroxyprogesterone caproate.

Makena (NDC 64011-243-01) is supplied as 5 mL of a sterile clear yellow solution in a multi-dose glass vial.

Each 5 mL vial contains hydroxyprogesterone caproate USP, 250 mg/mL (25% w/v), in castor oil USP (28.6% v/v) and benzyl benzoate USP (46% v/v) with the preservative benzyl alcohol NF (2% v/v).

Single unit carton: Contains one 5 mL multi-dose vial of Makena (250 mg/mL) containing 1250 mg of hydroxyprogesterone caproate.

Store at 20° to 25°C (68° to 77°F). Do not refrigerate or freeze.

Use multi-dose vials within 5 weeks after first use.

Caution: Protect vial from light. Store vial in its box. Store upright.

17 **PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Counsel patients that Makena injections may cause pain, soreness, swelling, itching or bruising. Inform the patient to contact her physician if she notices increased discomfort over time, oozing of blood or fluid, or inflammatory reactions at the injection site [*see Adverse Reactions (6.1)*].

Distributed by: AMAG Pharmaceuticals, Inc.
Waltham, MA 02451

02/2018
ver 1.2

PATIENT INFORMATION
MAKENA (mah-KEE-na)
(hydroxyprogesterone caproate injection)
auto-injector for subcutaneous use
MAKENA (mah-KEE-na)
(hydroxyprogesterone caproate injection)
vial for intramuscular use

Read this Patient Information leaflet before you receive MAKENA. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is MAKENA?
MAKENA is a prescription hormone medicine (progestin) used in women who are pregnant and who have delivered a baby too early (preterm) in the past. MAKENA is used in these women to help lower the risk of having a preterm baby again. It is not known if MAKENA reduces the number of babies who are born with serious medical conditions or die shortly after birth. MAKENA is for women who:
- Are pregnant with one baby.
- Have had a preterm delivery of one baby in the past.

MAKENA is not intended for use to stop active preterm labor.
It is not known if MAKENA is safe and effective in women who have other risk factors for preterm birth.
MAKENA is not for use in women under 16 years of age.

Who should not receive MAKENA?
MAKENA should not be used if you have:
- blood clots or other blood clotting problems now **or** in the past
- breast cancer or other hormone-sensitive cancers now **or** in the past
- unusual vaginal bleeding not related to your current pregnancy
- yellowing of your skin due to liver problems during your pregnancy
- liver problems, including liver tumors
- high blood pressure that is not controlled

What should I tell my healthcare provider before receiving MAKENA?
Before you receive MAKENA, tell your healthcare provider about all of your medical conditions, including if you have:
- a history of allergic reaction to hydroxyprogesterone caproate, castor oil, or any of the other ingredients in MAKENA. See the end of this Patient Information leaflet for a complete list of ingredients in MAKENA.
- diabetes or pre-diabetes.
- epilepsy (seizures).
- migraine headaches.
- asthma.
- heart problems.
- kidney problems.
- depression.
- high blood pressure.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

MAKENA may affect the way other medicines work, and other medicines may affect how MAKENA works.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I receive MAKENA?
- **Do not** give yourself MAKENA injections. A healthcare provider will give you the MAKENA injection 1 time each week (every 7 days) either:
  - in the back of your upper arm as an injection under the skin (subcutaneous), **or**
  - in the upper outer area of the buttocks as an injection into the muscle (intramuscular).
- You will start receiving MAKENA injections anytime from 16 weeks and 0 days of your pregnancy, up to 20 weeks and 6 days of your pregnancy.
- You will continue to receive MAKENA injections 1 time each week until week 37 (through 36 weeks and 6 days) of your pregnancy or when your baby is delivered, whichever comes first.

What are the possible side effects of MAKENA?
MAKENA may cause serious side effects, including:
- **Blood clots**. Symptoms of a blood clot may include:
  - leg swelling
  - redness in your leg
  - a spot on your leg that is warm to the touch
  - leg pain that gets worse when you bend your foot

Call your healthcare provider right away if you get any of the symptoms above during treatment with MAKENA.

- **Allergic reactions**. Symptoms of an allergic reaction may include:
  - hives
  - itching
  - swelling of the face

Call your healthcare provider right away if you get any of the symptoms above during treatment with MAKENA.

- **Decrease in glucose (blood sugar) tolerance**. Your healthcare provider will need to monitor your blood sugar while taking MAKENA if you have diabetes or pre-diabetes.
- **Your body may hold too much fluid (fluid retention)**.
- **Depression**.
- **Yellowing of your skin and the whites of your eyes (jaundice)**.
- **High blood pressure**.

The most common side effects of MAKENA include:
- pain, swelling, itching or a hard bump at the injection site
- hives
- itching
- nausea
- diarrhea

Call your healthcare provider if you have the following at your injection site:
- increased pain over time
- oozing of blood or fluid
- swelling

Other side effects that may happen more often in women who receive MAKENA include:
- Miscarriage (pregnancy loss before 20 weeks of pregnancy)
- Stillbirth (fetal death occurring during or after the 20th week of pregnancy)
- Hospital admission for preterm labor
- Preeclampsia (high blood pressure and too much protein in your urine)
- Gestational hypertension (high blood pressure caused by pregnancy)
- Gestational diabetes
- Oligohydramnios (low amniotic fluid levels)

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of MAKENA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store MAKENA?
- **MAKENA auto-injector for subcutaneous use**:
  - Store the auto-injector at room temperature between 68°F to 77°F (20°C to 25°C).
  - Do not refrigerate or freeze.
  - Protect the auto-injector from light.
  - Store the auto-injector in its box.
- **MAKENA vial for intramuscular use**:
  - Store the vial at room temperature between 68°F to 77°F (20°C to 25°C).
  - Do not refrigerate or freeze.
  - Protect the vial from light.
  - Store the vial in its box in an upright position.

Keep MAKENA and all medicines out of the reach of children.

General information about the safe and effective use of MAKENA.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use MAKENA for a condition for which it was not prescribed. Do not give MAKENA to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about MAKENA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about MAKENA that is written for health professionals.

What are the ingredients in MAKENA?
Active ingredient: hydroxyprogesterone caproate

Inactive ingredients: castor oil and benzyl benzoate. 5 mL multi-dose vials also contain benzyl alcohol (a preservative).

Distributed by: AMAG Pharmaceuticals, Inc.
Makena is a registered trademark of AMAG Pharmaceuticals, Inc.
For more information, go to www.MAKENA.com or call AMAG Pharmaceuticals Customer Service at the toll-free number 1-877-411-2510.

This Patient Information has been approved by the U.S. Food and Drug Administration Revised: 02/2018

PP-MKN-US-00452 02/18

EXHIBIT F

KERSHAW COOK & TALLEY PC

January 3, 2020

VIA CERTIFIED MAIL

William K. Heiden, President and CEO
AMAG Pharmaceuticals, Inc
1100 Winter St., Suite 3000
Waltham, MA 02451

Dear Mr. Heiden,

In compliance with the requirements of the California Consumers Legal Remedies Act (Civil Code §§ 1750, *et seq.*) we write on behalf of our client, Angele Nelson ("Claimant") and on behalf of all others similarly situated. Pursuant to Civil Code section 1782, you are hereby notified of the following:

In or around 2016 Claimant became aware that she was pregnant. After visiting her doctor, she was advised that she was at risk for premature birth. To reduce the risk of premature birth, her doctor recommended that she take the drug Makena. Claimant consented to the use of the drug and began the drug therapy in or around 2016. Because her insurance would not cover the full cost of the drug, Claimant paid out of pocket expenses for the therapy.

Prior to being prescribed Makena, AMAG highly advertised its effectiveness at preventing the risk of premature of birth. Specifically, on its website and in numerous marketing materials, AMAG made the following claims:

a. "Makena helps you get closer to term."

b. "Makena … is a hormone medicine (progestin) prescribed to lower the risk of having another preterm baby in women who are pregnant with one baby, and who've unexpectedly delivered one baby too early (before 37 weeks) in the past."

c. "Makena gives moms an extra layer of support."

d. "receiving the weekly injections of Makena is giving me the peace of mind knowing that I'm doing everything I can to help prolong this pregnancy."

e. "looking back, Makena gave me hope that I had a better chance of delivering Olivia full term."

f. "Makena … helps give bab[ies] more time to develop."

Such claims were likely to and in fact did deceive members of the public.

After taking and paying for Makena, Claimant ultimately discovered that all of the advertising claims concerning Makena were misleading and/or false. At this time, the results of a long term study to determine if Makena was effective was released to the public. According to AMAG, the study's results showed no "statistically significant difference between the treatment [Makena] and placebo arms for the co-primary endpoints." The results also showed there was no significant difference between subjects using Makena and subjects using placebos on the rate or neonatal mortality or morbidity. In other words, the Study showed that Makena, is no more effective than a placebo.

Claimant is informed and believes that thousands of other women in California were prescribed Makena and paid money (either out of pocket or through their insurance company, or both) for this drug that is no more effective than a placebo.

The conduct as described above violates various provisions of the CLRA including the following:

a. Using deceptive representations in connection with their goods or services, in violation of section 1770(a)(4);

b. Representing that goods or services have characteristics or quantities which they do not have, in violation of section 1770(a)(5);

c. Advertising goods or services with the intent to sell them not as advertised, in violation of section 1770(a)(9);

On behalf of our client, we hereby demand that you pay damages and refunds to any and all California consumers who purchased Makena. If within thirty (30) days after receipt of this Civil Code section 1782 notice, you have not adequately addressed the wrongful conduct described above, Claimant will seek relief in the form of damages and other appropriate relief under the Civil Code section 1780 for herself and all other similarly situated individuals.

If you would like to discuss this issue further, please feel free to give us a call.

Very truly yours,

KERSHAW, COOK & TALLEY PC

STUART C. TALLEY

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KERSHAW COOK & TALLEY

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